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Journal of the AMERICAN MEDICAL WOMEN'S ASSOCIATION

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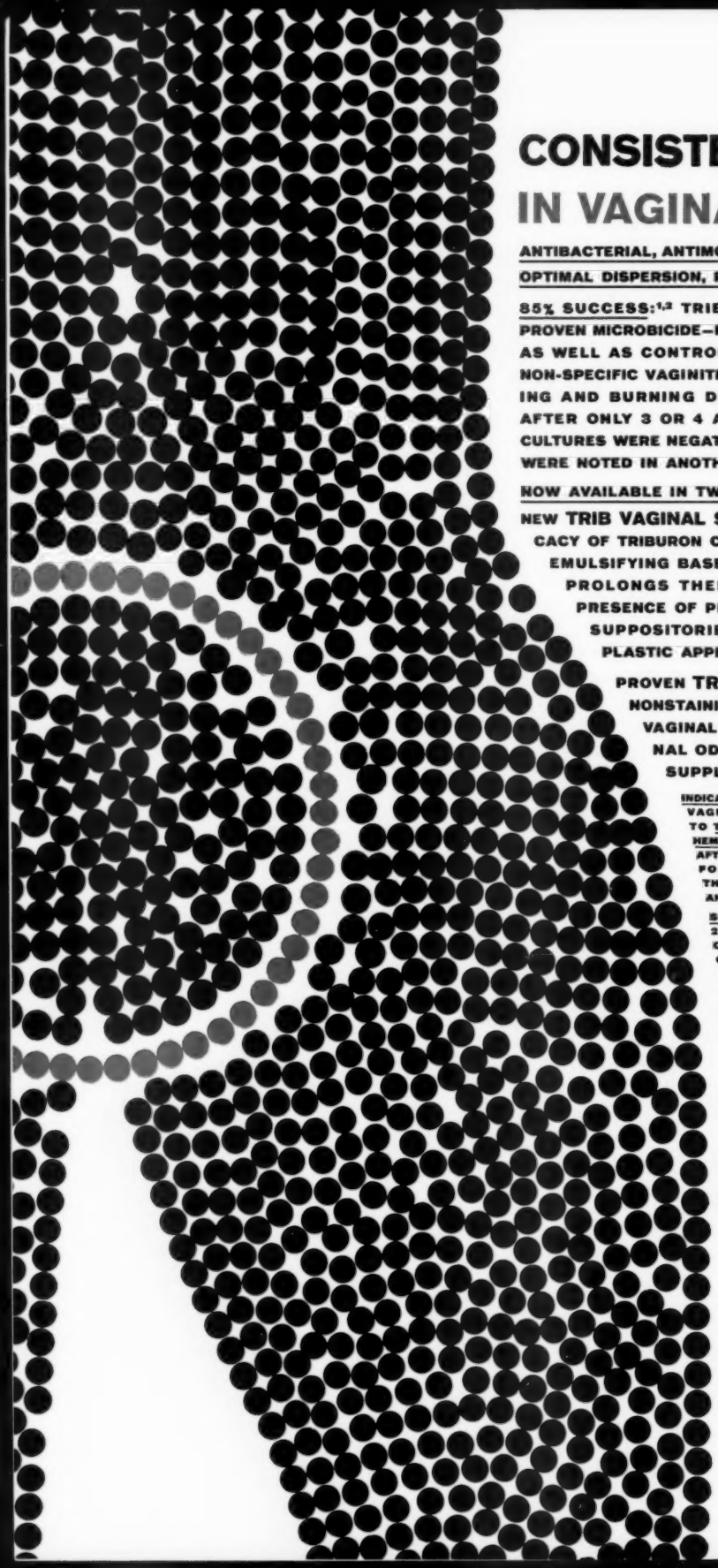

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REFERENCES: 1. N. MULLA AND J. J. McDONOUGH, ANN. NEW YORK ACAD. SC., 82:(ART. 1), 162, 1959. 2. L. E. SAVEL, D. B. GERSHENFELD, J. FINKEL AND P. DRUCKER, IBID., P. 166.

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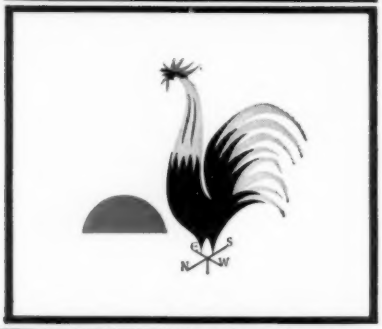

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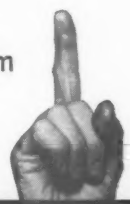

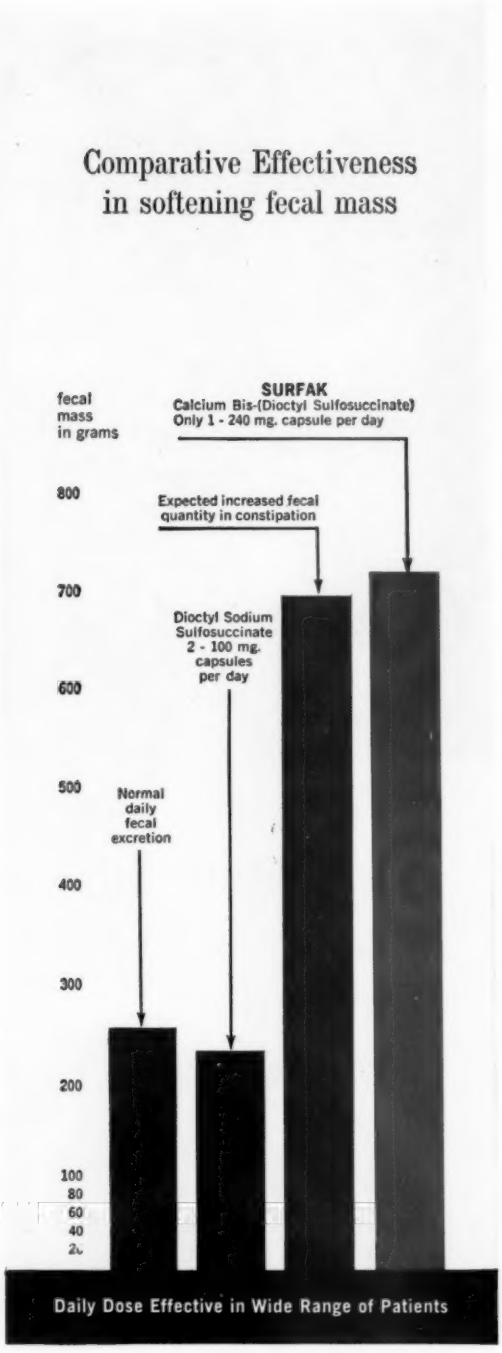

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CIBA
SUMMIT, N. J.

*Coan, J. P., McAlpine, J. C., and Boone, J. A.: J. South Carolina M. A. 51:417 (Dec.) 1955.

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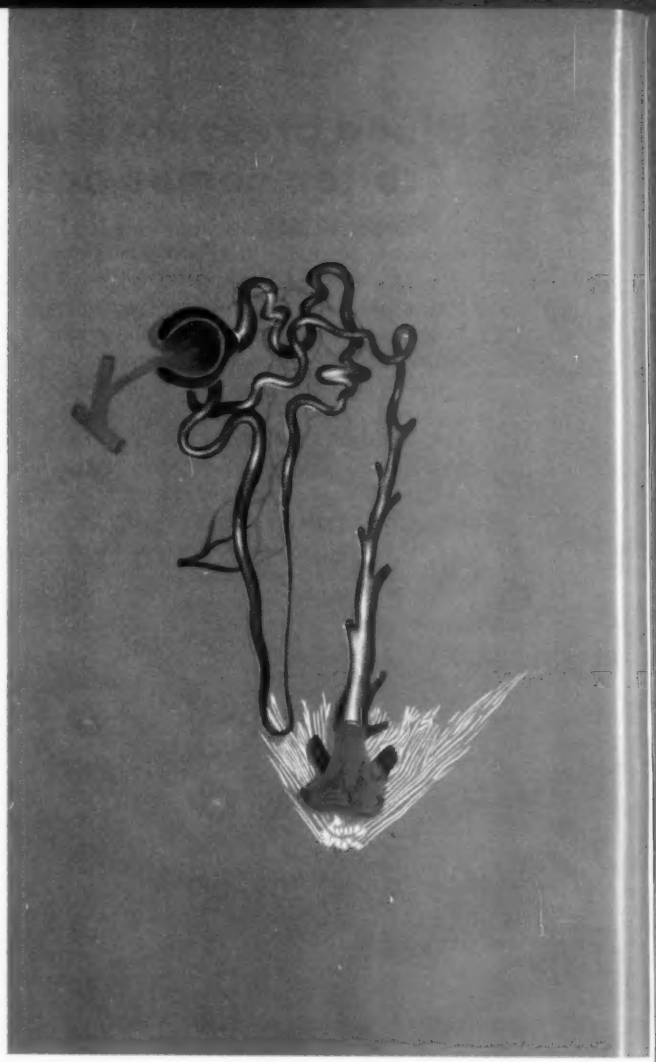

on the pathogenesis of pyelonephritis:

"An inflammatory reaction here [renal papillae] may produce sudden rapid impairment of renal function. One duct of Bellini probably drains more than 5000 nephrons. It is easy to see why a small abscess or edema in this area may occlude a portion of the papilla or the collecting ducts and may produce a functional impairment far in excess of that encountered in much larger lesions in the cortex."[1]

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References: 1. Schreiner, G. E.: A.M.A. Arch. Int. M. **102**:32, 1958. 2. Freedman, L. R., and Beeson, P. B.: Yale J. Biol. & Med. **30**:406, 1958. 3. Rocha, H., et al.: Yale J. Biol. & Med. **30**:341, 1958.

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*Kearney, R. D.: Current Therap. Res. 2:127, April, 1960.

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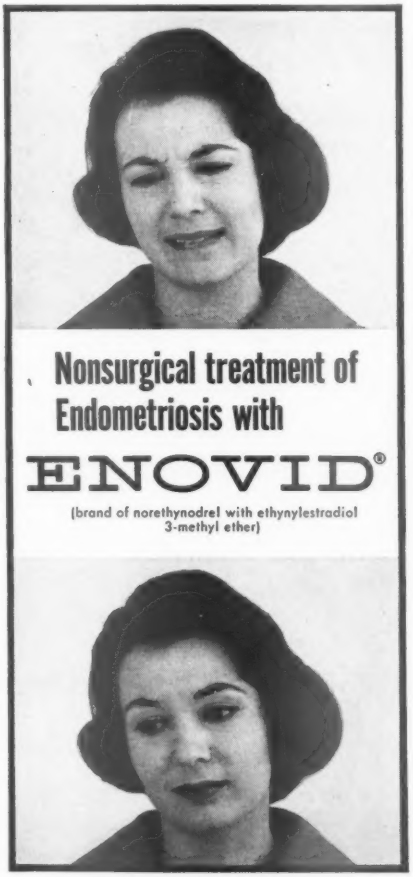
References:

1. Friend, D. G.: Current Drug Therapy: The Phenothiazines; Clin. Pharm. & Therap. 1:5 (Jan.) 1960. 2. Kistner, R. W.: Endometriosis and Infertility, Clin. Obst. & Gynec. 2:877 (Sept.) 1959. 3. Wilson, L. A., Trichomonas Vaginalis Vaginitis, in Conn, H. F.: Current Therapy—1960, Philadelphia, W. B. Saunders Company, 1960, p. 657. 4. Kupperman, H. S., The Choice of Drugs in Endocrine Dysfunction, in Modell, W.: Drugs of Choice 1960-1961, St. Louis, The C. V. Mosby Company, 1960, p. 584. 5. Goldfarb, A. F., and Napp, E. E.: Use of Methallenestril (Vallestril) in Control of Menopausal Symptoms, J.A.M.A. 161:616 (June 16) 1956.



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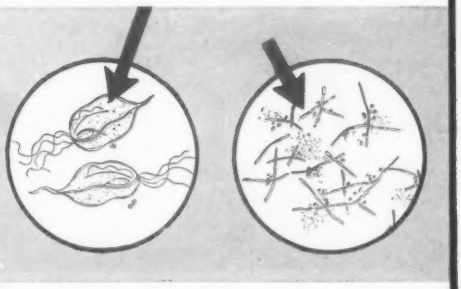

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*Rock, J.: Garcia, C. R., & Pincus, G.: *Am. J. Obst. & Gynec.* 79:758, 1960.

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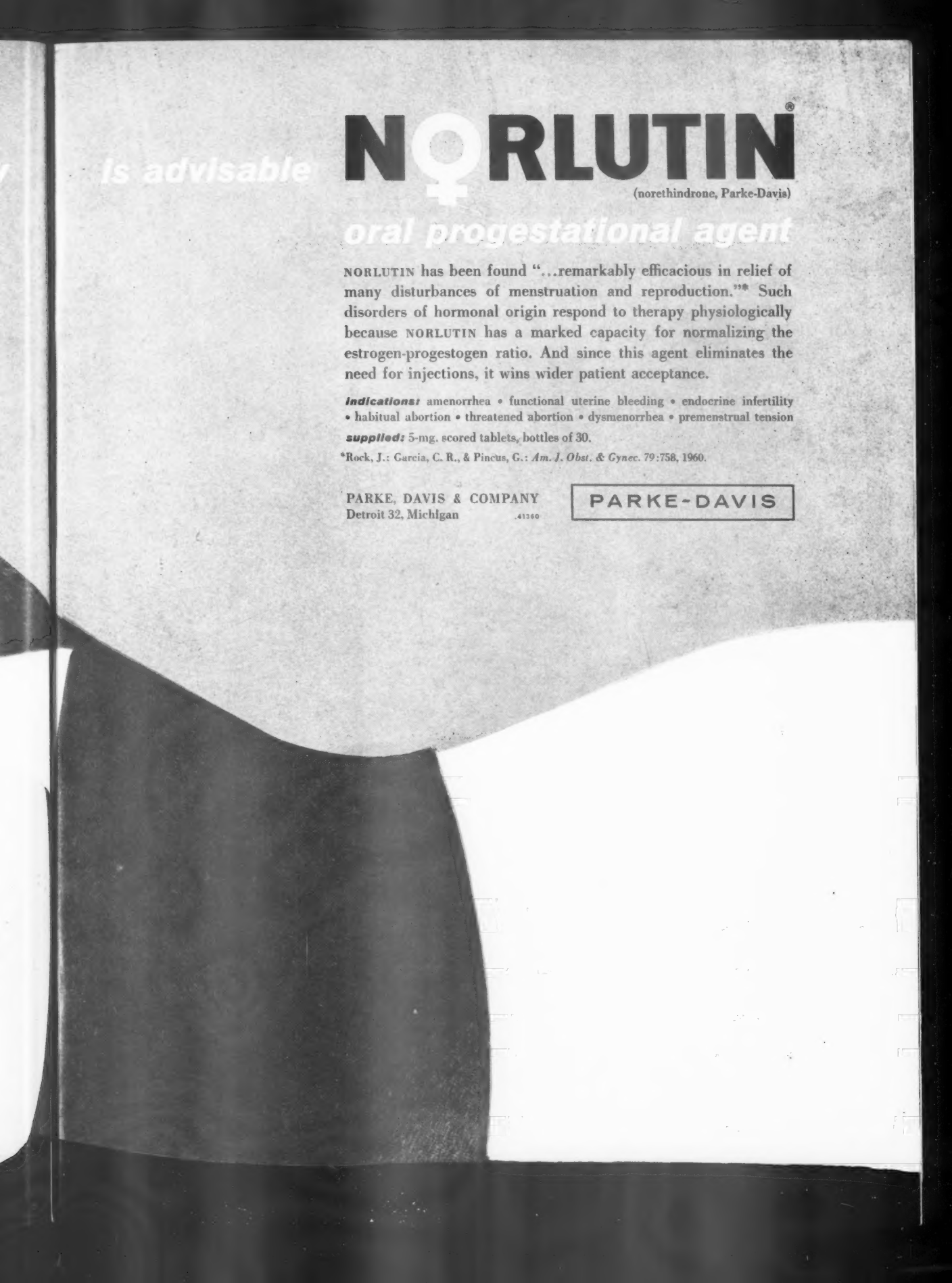

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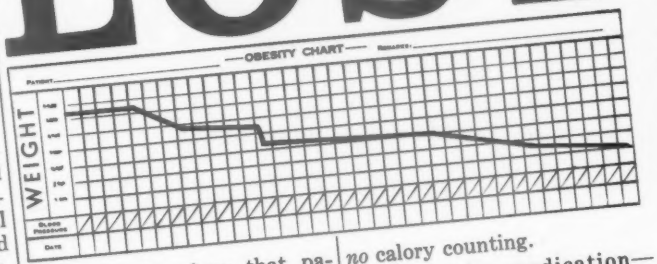

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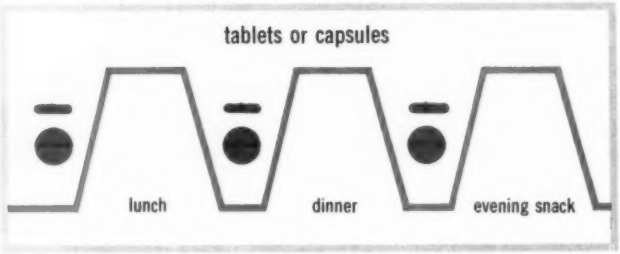

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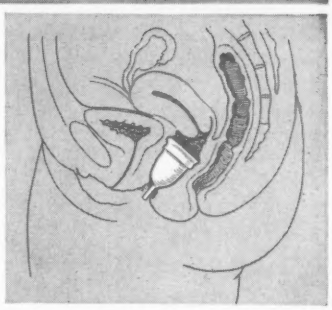

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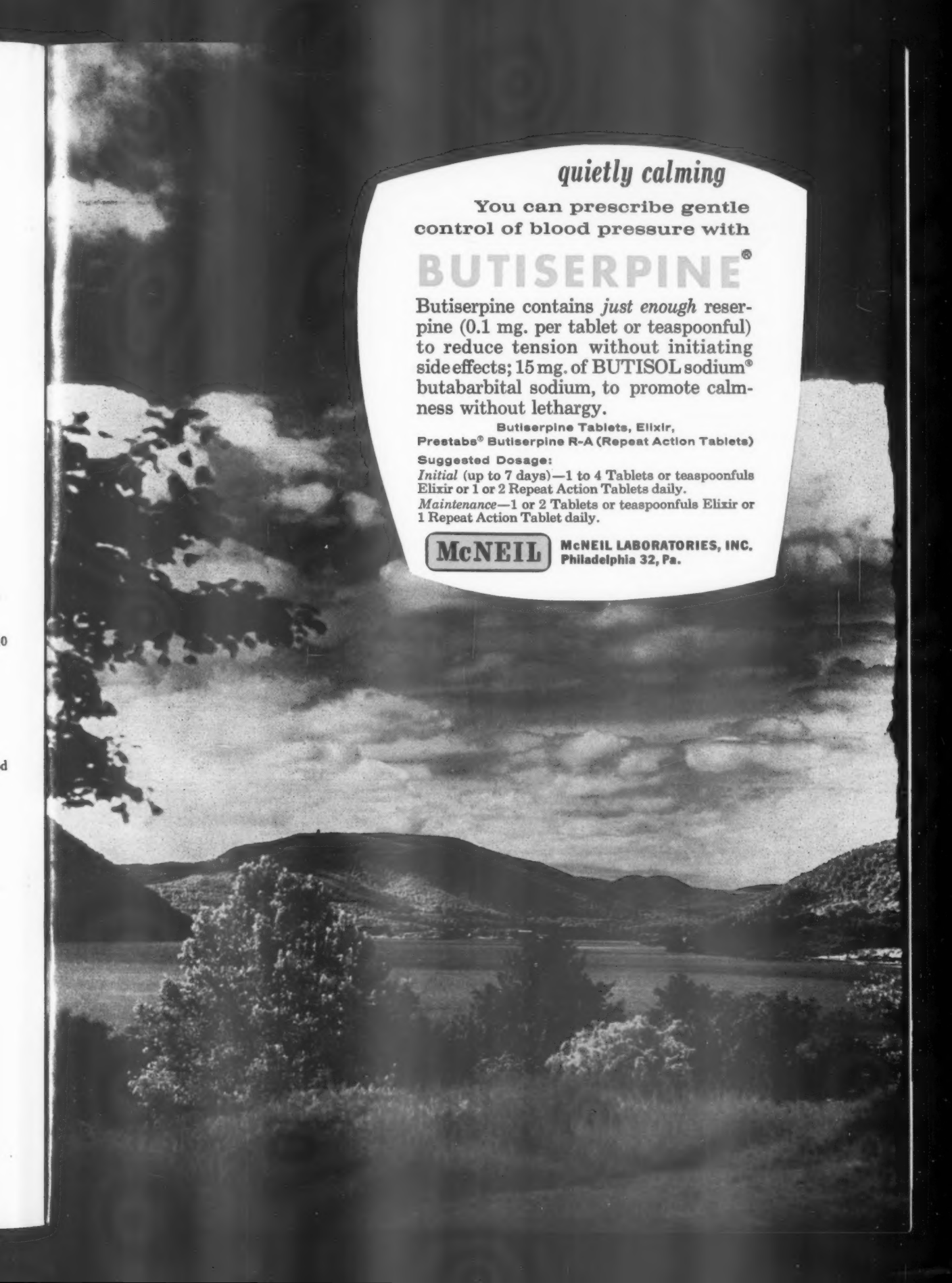
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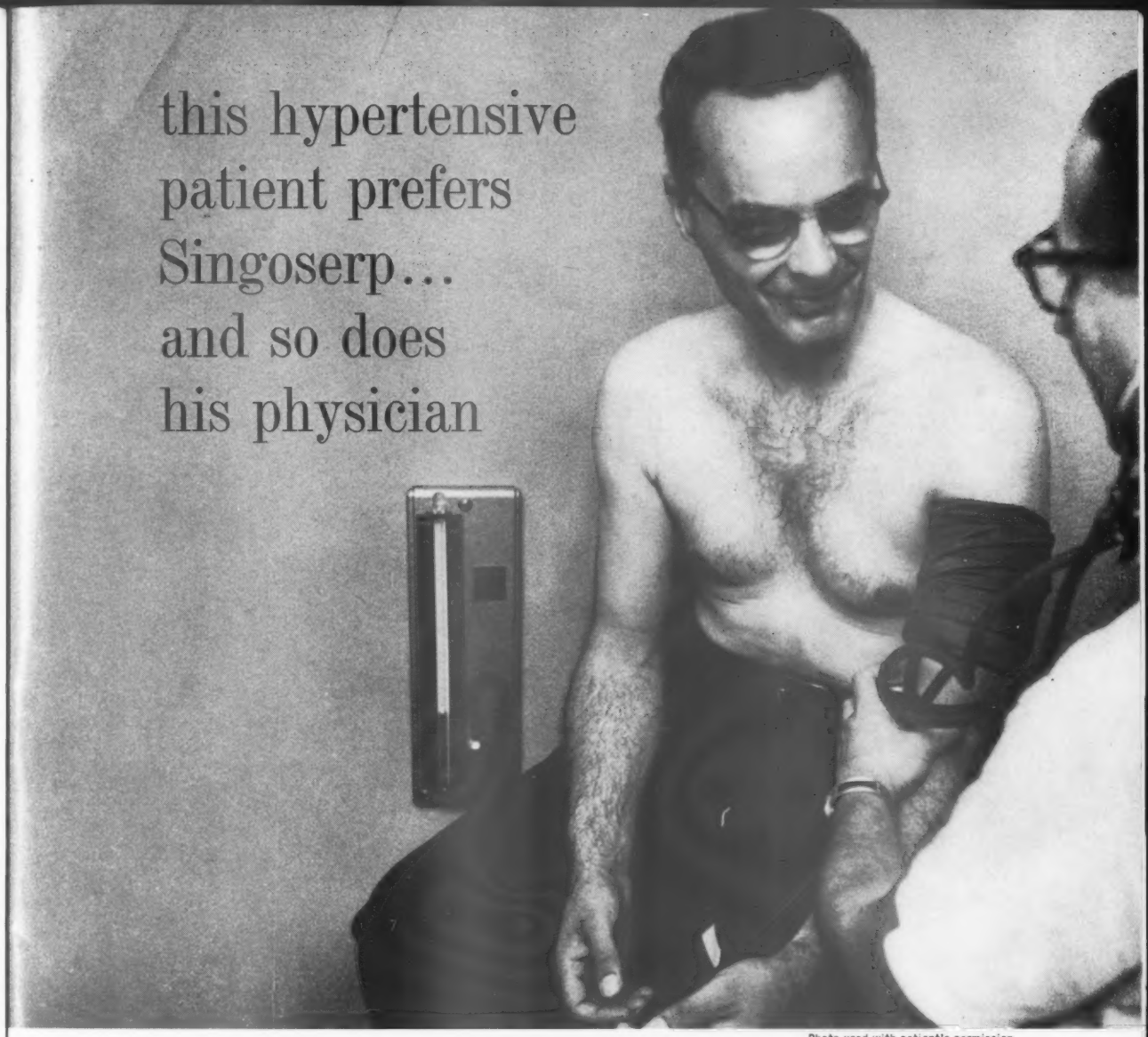

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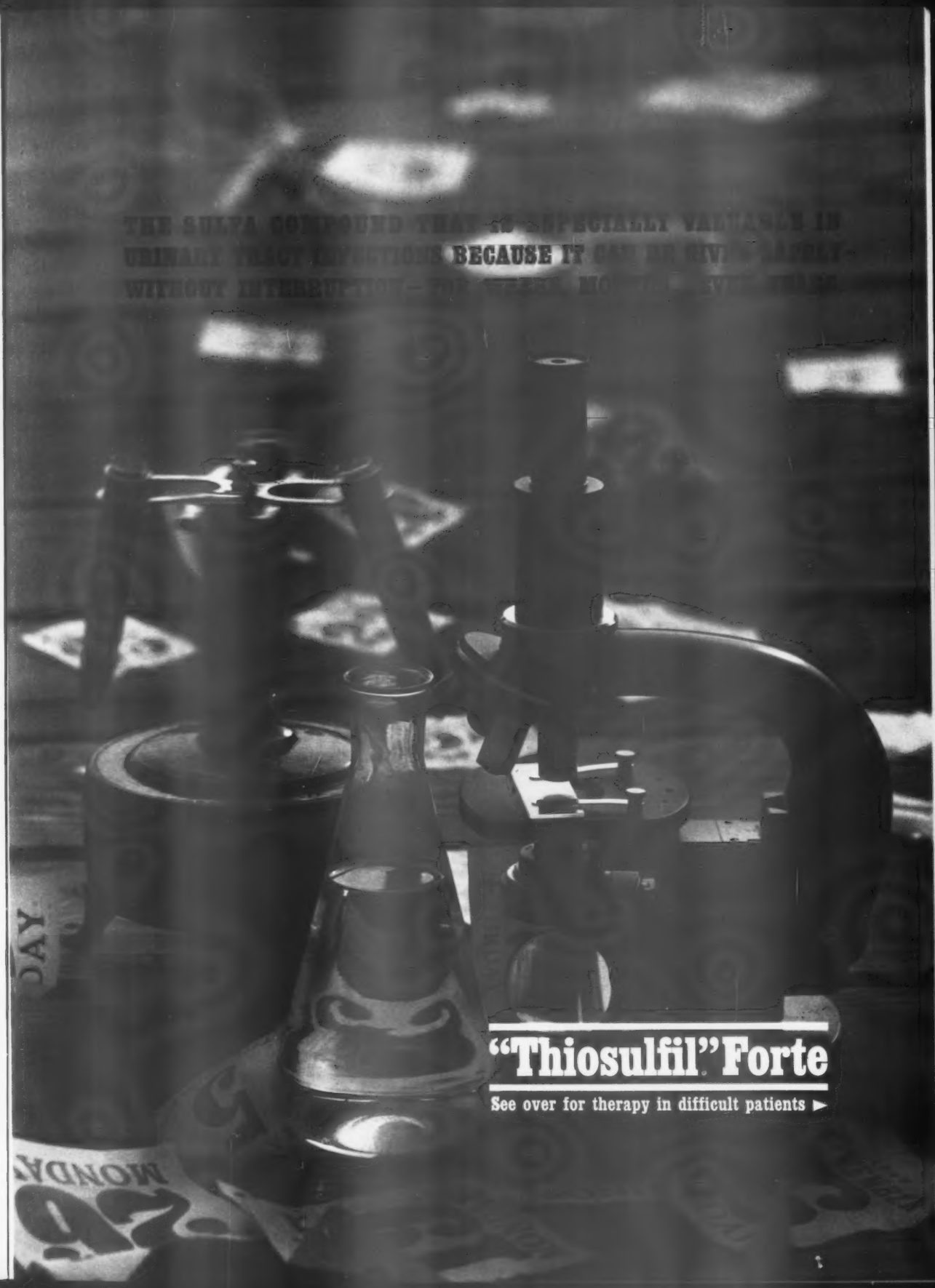

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In acutely infected patients: Results of seven years' clinical experience:[1] Bourque's report covers 3,057 patients treated with "Thiosulfil" for upper and lower urinary tract infections. The causative organisms were E. Coli, Pseudomonas, Klebsiella, Enterococcus, Staphylococcus, Alcaligenes fecalis, and Proteus.

The results obtained were 76 per cent excellent; 11 per cent fair. In cystitis of short duration and without urinary obstruction 100 per cent good results were reported. average dosage: 3 Gm./day for 2 weeks

in pathologic conditions that cannot be cured 38 cases of chronic urinary tract infection:[2] "The cause of the infection in 25 cases was residual urine due to lower urinary tract disease, which for some reason could not be eliminated, such as prostatic carcinoma or hypertrophy (16 cases), vesical diverticulum or hypotonia (6 cases). Chronic upper urinary tract infection was present in 22 cases, some of which were secondary to the lower tract obstructive lesions."

"The results of treatment were as follows: Good, 17 cases, urine became clear and symptoms subsided while under treatment; fair, 10 cases, infection reduced and symptoms became less or subsided; poor, 11 cases, no evident change in urine or symptoms." initial dosage: 2 Gm./day

52 paraplegics with g.u. infections:[3] "Urinalysis reverted to normal in 53 per cent of the 'Thiosulfil' group . . ."

" 'Thiosulfil' was ineffective in only 7 per cent . . ." dosage: 2 Gm./day

RECORD OF SAFETY

Only these few side effects have been reported with "Thiosulfil." Out of 52 paraplegic cases . . . only one instance of dermatitis.[3] Out of 50 cases . . . mild reactions consisted of slight gastric distress (1); flatulence (3); rash (1); pruritus (1); transient crystalluria (2).[4] Out of 38 cases of chronic infection . . . mild reactions of: stomach and eye discomforts (1); dizziness (1); slight diarrhea (1).[2] Out of 100 cases . . . one reaction—nausea.[5] Out of 3,057 cases . . . 47 patients (1.6%) showed g.i. disturbances and 33 patients (1.1%) allergic reactions.[1] Out of 300 cases . . . one reaction (appetite loss and lassitude).[6] NO REPORTS OF: hemorrhagic dyscrasias, hematuria, anuria, agranulocytosis.

The Sulfa Compound Used Successfully Without Interruption for: one month;[3,4] more than 6 weeks;[2] 90 days;[5] 18 months;[3] 5 to 6 years.[7]

DOSAGE (Urinary Tract Infections)

TIME PERIOD	DOSE
First two weeks	3 Gm./day[1]
2 weeks to 3 months	2 Gm./day[3,4]
3 months or longer	0.5 Gm./day[7]

Suggested Range of Dosage: 1 or 2 tablets three or four times daily. Note: The usual precautions exercised with sulfonamides should be observed. Supplied: No. 786—Bottles of 100 and 1,000 scored tablets. Each tablet contains 0.5 Gm. sulfamethizole.

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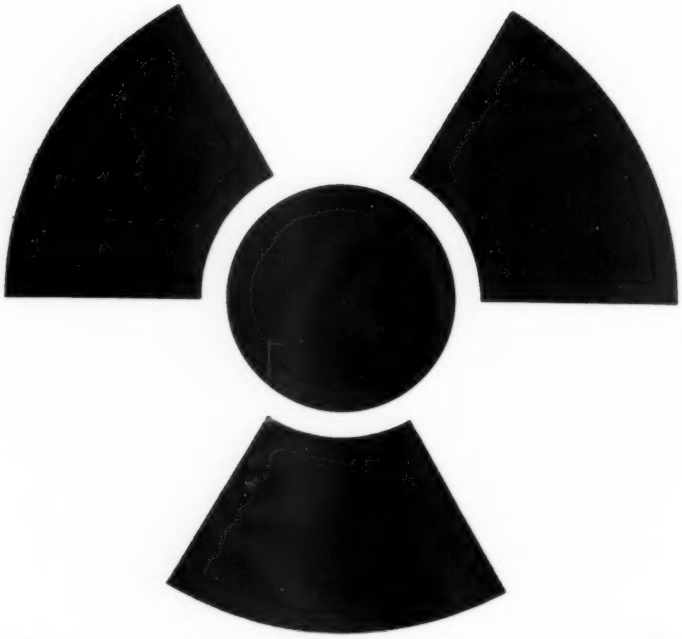

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Recent Advances in Repository Therapy in Allergy*

Mary Hewitt Loveless, M.D.

THE AIM OF THE STUDIES to be discussed in this article is twofold. First, it has become apparent that it would be an asset to increase the proportion of the aqueous, or extract, phase of the water-in-petrolatum emulsion I introduced into allergy 14 years ago, and described in a preliminary report in 1947.[1] This would permit the use of more dilute, and hence more slowly diffusing, allergenic solutions if only a single extract is desired, or the combination of several solutions when multiple allergens are a seasonal problem, as in our Middle West. Having located by preliminary experiments a promising new formula in this direction, my second goal was to produce a uniform, large batch of ragweed emulsion that could be dispensed in sterile, needled, ready-to-use syringes and that would withstand the temperatures ordinarily encountered in interstate shipping. This would preclude the current need for the allergist to procure training and special equipment to prepare his own emulsion. It would place the responsibility for accuracy and sterility on a highly specialized staff and would offer physicians a source of uniform material for clinical evaluation of this new therapeutic procedure.

The first goal was met by setting up a battery of experimental emulsions of graduated proportions and by observing their stability under different temperatures during a period of many weeks; a presentation of detailed results, however, would exceed the scope of this

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paper. Suffice it to say that the most promising of the formulas (proportions of stabilizer: oil: water being 1:6:5, which will be explained later) was used in conjunction with the second goal, which was met when Wyeth Laboratories of Philadelphia generously agreed to provide me and a small group of collaborating allergists with single-dose, prepackaged 1:6:5 ragweed emulsion made according to my prescription, and to ship it to us in Tubex syringes ready for use in our ragweed-allergic patients during June, 1960. They also glycerinated some of the low-ragweed extract prepared for these treatment sets for use in preliminary and postseasonal instillation tests of our patients' eyes. Although I do not have all the results of the other allergists as yet, and the clinical outcomes must obviously await the ending of the current pollinating season, I do have, for presentation at this writing, sufficient material to compare the safety and stability of the new formula with that of a standard one I have used for the past 14 years, as well as with one more recently advocated by Dr. Ethan Allan Brown (1:9:10). The relative merits of manual and mechanical emulsification can also be compared for both these formulas, and the advantages of the prepackaged, individual treatment set can now be stated. Finally, the possible prognostic value of a microscopic analysis of an emulsion's droplet size distribution, of the gross appearance of an emulsion, of its activity when applied to a scratch in the skin, and of its stability under various temperatures during storage can now be estimated. Some suggestions for modification in dosage will also be made, with a view toward eliminating undesirable overdose reactions occasionally encountered in the recipients of emulsion.

HISTORICAL BACKGROUND

As reported in this journal several years ago,[2] the concept of retarding and prolonging the release of vaccine from its injection site was intensively exploited by Freund in animals during the early 1940's. He found that the emulsification in mineral oil of such antigens as typhoid vaccine not only enhanced the resulting antibody output but made it more persistent, particularly when he also included acid-fast organisms. To encourage stability of the emulsified state he incorporated a surface-active agent like Falba (a mixture of beeswax, paraffin oils of varying viscosities, and oxycholesterols extracted from lanolin, dispensed by Pfaltz and Bauer of New York City), which possesses both hydrophilic and hydrophobic qualities enabling it to attract water as well as oil. Since this in effect created a mantle of oil about each droplet of water and tended to negate the cohesive forces that would otherwise have led to coalescence and separation of the water from the oil, it slowed the rate of diffusion of the watery phase from the injection site out into the surrounding body fluids. The prolongation of residence of the vaccine in the body, plus additional adjuvant effects contributed by the inert petrolatum and the killed acid-fast bacilli, accounted for the enhanced immunological effect. The retardation in release of the aqueous component was responsible for another phenomenon; that is, animals were found to tolerate nearly 10 lethal doses of botulinus toxin if the latter were emulsified in mineral oil prior to the parenteral challenge.

Following these leads, the writer demonstrated that she could inject her pollen-allergic volunteers with tenfold to twentyfold more units of allergen when it was emulsified in petrolatum than when it was given in plain form. This made it feasible to restrict annual preventive treatments to one preseasonal visit a year. During the years that followed this initial experiment of 1947, the amount of allergen involved in annual treatment was gradually increased to as much as 10,000 "protein" nitrogen units while, at the same time, the three to five divided doses used at the outset became routinely reduced to one. Statistical analysis of the adverse reaction rates as well as clinical resistance data indicated that the abbreviated procedure was as safe and as effective as long courses of weekly injections had been for the individuals in question. Meanwhile, the repository principle had also been successfully applied to many other types of inhalant allergy. Throughout these experimental years, an objective immunological test has been utilized before and after each annual treatment. It is comprised of an instillation test of the patient's eye, which affords the allergist a clue to the degree of hypersensitivity that exists. For this reason it is not surprising that the minimal reactive strength of extract, as determined by the test, serves as a crude index to the amount of allergen that the patient will tolerate in his repository injection. Tests of the skin accomplish this far less reliably.

At the present time there is widespread in-

terest in the repository method among allergists. Not only have several hundred learned the techniques of preparation and administration of emulsion by spending two or more days in my office during periods of intensive therapy of this type but an official evaluation is being made this fall by the American Academy of Allergy under the leadership of Dr. Samuel Feinberg. This program involves some 30 allergists in various sections of the United States and possibly several thousand volunteer hay fever sufferers. Before emulsified allergen becomes generally available, however, it will be necessary for some institution interested in supplying it commercially to make application for a permit to ship this injectable material across state lines. The official licensing agency of the Government in Washington, D.C., will, of course, have to be convinced of the effectiveness and safety of the material before granting this permission. There is no evidence for the possible carcinogenicity of the mineral oil-Arlacel A component.[3]

MATERIALS AND METHODS

Pollen Extract. Except for the fact that as much as 20 Gm. defatted pollen was subjected to extraction with each 100 cc. alkaline saline solution (Coca's extracting fluid) to ensure a yield of about 200,000 "protein" nitrogen units per cubic centimeter, the preparation of low-ragweed pollen extract was carried out in a conventional manner. An aliquot of the finished product was admixed with an equal volume of sterile glycerin for the purpose of doing conjunctival instillation tests with a stable extract.

Preparation of Emulsions. The unglycerinated portion of the recently made ragweed extract had to be variously diluted (in isotonic saline solution) according to the proportion of aqueous phase specified for the several emulsion formulas. Since the standard strength of all emulsions except the Brown variety was 10,000 units per cubic centimeter, it was necessary to use extract of 24,000 units per cubic centimeter in preparing the 1:6:5 formulas and extract of 60,000 units per cubic centimeter for the 4:6:2 type. Instead of employing one standard emulsion in different volumes for his small, average, and large doses as I do, Dr. Brown prefers to administer a constant volume of 1 cc. in all instances, controlling the dose by varying the concentration of extract in successive preparations. Hence, for the 1:9:10 formulas, I prepared one with 20,000 unit extract, the resulting emulsion containing 10,000 units per cubic centimeter. A second preparation called for 15,000 unit extract, while the weakest emulsion utilized 10,000 unit solution.

When the Brown emulsion was being prepared, it was necessary to use Drakeol mineral oil (Pennsylvania Refining Company), which is of slightly lower viscosity than Atreol no. 9, the standard petrolatum product that I use (marketed by Atlantic Refining Company of Newark, N.J.). Arlacel A (Atlas Powder Corporation of Wilmington, Del.) was the stabilizer chosen for all emulsions because it is a simple chemical substance, mannide monooleate, in contrast to Falba, which is a heterogeneous mixture of uncertain composition.

Manual emulsification was carried out with a 2 cc. tuberculin-type syringe that had been fitted tightly with a blunt-tipped 15 gauge needle. The blunted needle was held firmly against the bottom of the Wassermann tube containing the Arlacel A, mineral oil, and pollen extract in appropriate volumes for the formula being made. The three components were then pumped manually back and forth from the tube into the syringe, as forcibly and as rapidly as possible for exactly six minutes. Of the total volume of 3 to 3.6 cc. in each tube, about 2 cc. were then drawn up into the syringe for future therapeutic use. A ½ in. 26 gauge needle was substituted for the large mixing needle, the latter being dropped aseptically into the emulsion tube in readiness for future withdrawals. The filled syringe was protected by slipping a sterile Wassermann tube over its needled end, and the unit was then placed in the refrigerator until used some hours to weeks later. In no instance was reemulsification attempted, with the exception of the 1:9:10 preparation, which proved to be rather poorly tolerated by patients, particularly when prepared mechanically.

Mechanical emulsification was of two types. Dr. Brown's device was used for the Drakeol emulsions of 1:9:10 formula, and I am indebted to Dr. Harold Lecks of Philadelphia for all these preparations. Three hundred cycles, involving over an hour's time for each 4 cc. batch, were required to produce an emulsion that was satisfactory in appearance microscopically. The three different strengths of emulsion were aseptically loaded in plastic, disposable syringe and needle sets. A personal messenger delivered the supply to me in New

York on the following morning. A number of the preparations were subsequently subjected to my routine manual emulsification just prior to therapeutic use, because of the development of unusually strong adverse responses in 2 of the first patients to receive this material.

The second type of mechanical emulsification was carried out by Wyeth Laboratories in Philadelphia. With about 800 cc. of the three standard components used in my 1:6:5 manual emulsions, they subjected the materials to one and a half minutes of intensive homogenization in a Waring Dispersall kept at low temperature with the aid of ice packing. After 21 days of negative sterility test readings, the entire batch was introduced into Tubex cartridges in a volume of about 1.2 cc. each, a ½ in. 25 gauge needle being fitted to the tip, which was maintained in a sterile state by means of a neoprene sheath. These cartridges were shipped to me and to a small group of collaborators through the mail and were stored in the refrigerator until used as much as 48 days later without any further manipulation.

Tests for sterility were carried out in thioglycolate broth in the case of every emulsion used by me. The purpose was not only to assure sterility but also to afford an opportunity for observing the drop of emulsion for globularity and homogeneity during the 21 day reading period advocated for such emulsions. (Incubator temperatures encourage separation.)

Microscopic examination was made of one drop to nine drops that were extruded through the needle to be used during injection of the repository. The number of drops that were extruded depended on the readiness with which a drop that maintained its inverted cone shape on the slide was procured. If considerable creaming, or separation of oil, had taken place, as many as nine were sometimes needed. The next drop was placed on a small scratch in the prospective recipient's forearm, for comparison with similar applications of other emulsions and with nonemulsified extract in strengths of 160, 1,280, and 10,240 units per cubic centimeter, as well as with emulsified isotonic saline solution. Results were traced at 20 minute periods to provide permanent records.

Eye tests were carried out as in the past,[1] the first strength being 10 units per cubic centimeter. A succession of doubling strengths was employed at five minute intervals until minimal reddening and itching developed to serve as the end point. Class A patients responded to extract of 10, 20, or 30 unit strength and were assigned to a therapeutic dose of emulsion of 5,000 units. Class B subjects gave the threshold response to strengths ranging from 40 to 240 units per cubic centimeter and were accordingly assigned a dose of 7,500 units. Those requiring 320 or stronger solutions were graded as class C cases and were given the allotted dose of 10,000 units.

Patients accepted into the experimental group all gave an unequivocal history of ragweed pollen allergy (some had never been treated before) and all responded to extract of no greater strength than 10,240 units per cubic centimeter. Ages ranged from 4 to 74 years, both sexes were represented, and assignment to the type of emulsion was strictly random. In short, the first individual to appear in the office with a given eye test requirement (such as 10 units or 120 units) was assigned to the 1:6:5 manual preparation, the second found with this exact requirement received the same formula but with the mechanically prepared Tubex cartridge, the third was given a manually made 1:9:10 emulsion, and so on. After about 20 treatments had been completed with each of the three formulas, the number of patients assigned to the Tubex method was doubled, then tripled, since this preparation was my chief interest in 1960.

FINDINGS

Table 1 gives a bird's-eye view of the sensitivity distribution of patients assigned to the several emulsions. Of particular interest are the figures in the class A columns—it has long been apparent to me that this class is responsible for most of the adverse reactions encountered after any form of specific allergenic therapy. The Tubex preparation was assigned to a higher proportion of class A reactors (13 per cent of the 60 patients given this type of emulsion) than were the other types of emulsion. Its manual counterpart took second place in this regard, with the classical Brown emulsion being third. There were no patients of class A reactivity in the small group assigned to manually prepared 1:9:10 emulsion, nor were there any among the 21 patients given my long-established 4:6:2 formula. This defect was partially compensated for, however, by allotting greater proportions of class B reactors (especially to 40 and 80 units) to these two groups.

Risk of Overdose Reaction. Table I gives the incidence of adverse reactions to the five types of emulsion employed for the 128 ragweed-allergic subjects. To simplify comparisons, incidence has been expressed in terms of percentage—the number of reactions that presumably would have been encountered had each group contained 100 members. This was necessary because the number of persons assigned to the several groups varied.

Borderline manifestations were so minor that often the patient exhibiting them was unaware of them—erythema of the palms or ears, a few scattered hives, or a few sneezes. They subsided spontaneously usually within 30 minutes and showed that the dose selected for treatment had been almost ideal, representing essentially a "maximal tolerated dose." In theory, the latter should afford the patient his greatest chance for optimal clinical immunity without undue risk. The relatively low incidence listed for the 1:6:5 and the 4:6:2 manually prepared emulsions suggests that the release rates of these repositories were somewhat slower than for the other preparations. A contributing factor to the high incidence of borderline reactions among those receiving the mechanically mixed 1:9:10, and especially the Tubex 1:6:5, emulsions may have been the greater than average ages of the preparations when injected. The Wyeth preparations were 1 to 48 days old on the day of use and were never subjected to re-emulsification. The 1:9:10 Drakeol emulsions ranged from 1 to 17 days in age when injected in original form. Subsequent treatments with the latter material were preceded by a secondary manual mixing for six minutes just before use in an effort to lower the extraordinary reaction rate it produced. Other preparations were 0 to 7 days old when used.

"Slight" adverse responses, as compared with borderline responses, consisted of more extensive erythematous or urticarial reactions, mild hay fever, or suggestive asthma, requiring orally given antihistamines but not epinephrine by needle during the 4 to 48 hours of their persistence. Whereas about 17 per cent of the other groups exhibited such developments, it will be noted that there were none associated with the 4:6:2 long-used formula and only 5 per cent with the Tubex material. The only variety to elicit one slight-to-bad reaction and one bad was the ready-to-use emulsion sent by Dr. Lecks after he had prepared it in the Brown emulsifier. The more severe of these two reactions was the most intense in my 14 year experience with emulsion; hospitalization was necessary to control the marked bronchospasm diagnosed by a local internist consulted in my absence. Hives were also a problem for several days in this 14 year old boy, who had reacted by eye-test to 160-unit ragweed extract and had been given the regular dose of 7,500 units in a single injection under the skin. The later development of the slight-to-bad reaction in a young woman also of class B led me to prohibit further use of the material in persons of low conjunctival reactivity and to subject the emulsion to manual re-emulsification just before use. Even under these circumstances, three mild reactions were encountered. Allotment of the manually prepared, Atreol-containing 1:9:10 counterpart was also restricted to a small group of only 6 subjects as a precautionary measure. No reactions of greater than slight intensity were engendered in the latter.

The incidence of definite focal reactions to the Tubex method was found comparable with that noted for my 4:6:2 formula during the past decade (about 5 per cent). Patients receiving the 4:6:2 formula proved to be essentially reaction-free in 1960. The rate was clearly excessive, however, in those receiving the 1:9:10 emulsions as well as the manually mixed 1:6:5 material, particularly when the former had been mechanically produced. One can conclude that the 4:6:2 and the mechanically made 1:6:5 emulsions carried the lowest risk of adverse reaction and were therefore the safest types for therapeutic use.

Attempts To Set Up Criteria for a "Safe" Emulsion. On the day of injection each emulsion was subjected to three types of test: a direct scratch test on the recipient's forearm, microscopic examination for droplet size under high-dry magnification, and exposure of any emulsion left over after treatment to a shelf test at one of four temperatures until separation was noted. The following conclusions were reached.

Scratch Tests: By comparing the wheal-and-flare responses of the forearm to three strengths of nonemulsified ragweed extract (160, 1,280 and 10,240 units per cubic centimeter) and to the five therapeutic emulsions, it was estimated that about 100 units were being released from the Tubex material while slightly less than this was diffusing out of each of the others except for the mechanically mixed 1:9:10 emulsion (this was always

TABLE I

Incidence of Adverse Reactions to Treatment with Ragweed Emulsions of Several Types

No. Patients Treated	Formula of Emulsion Used in Therapy	Method Used To Emulsify Extract in Petrolatum	Distribution of Eye Test Sensitivity Classes, U./cc.						Adverse Reactions to Emulsion After Injection							
			Class A (10-30 U.)		Class B (40-240 U.)		Class C (320-10,240 U.)		Borderline		Slight		Slight-Bad		Bad	
			No. Cases	% of Group	No. Cases	% of Group	No. Cases	% of Group	No. Cases	% of Group	No. Cases	% of Group	No. Cases	% of Group	No. Cases	% of Group
24	1:6:5*	manual† (6 min.)	2	9	13	54	9	38	2	9	4	17	0	—	0	—
60	1:6:5* Tubex	Dispersall‡ (1½ min.)	8	13	29	48	23	38	16	27	3	5	0	—	0	—
17	1:9:10 (Drakeol) 1 cc.	Brown Emulsators§ (over 1 hr.)	1	6	10	59	6	35	3	18	3	18	1	6	1	6
6	1:9:10 1 cc.	manual (6 min.)	0	—	4	67	2	33	2	33	1	17	0	—	0	—
21	4:6:2‖	manual (6 min.)	0	—	17	81	4	19	1	5	0	—	0	—	0	—

*Arlacel A, 1 part: Atreol no. 9 mineral oil, 6 parts; and ragweed extract, 24,000 U./cc., 5 parts.

†Constituents were pumped back and forth with maximal force and speed with a 2 cc. tuberculin-type syringe to which a pointless 15 gauge needle was firmly attached and held firmly against the bottom of the Wassermann tube.

‡Waring commercial homogenizer for large volumes of material to be emulsified.

§This entire preparatory procedure was in accordance with the instructions of Dr. Brown; that is, 1 part of Arlacel A was added to 9 parts of Drakeol, a light mineral oil. Ten parts of ragweed extract of 20,000 U./cc., 15,000 U./cc., or 10,000 U./cc. were then introduced into the Drakeol-petrolatum mixture (depending on whether the patient was to receive 10,000 units, 7,500 units, or 5,000 units in a final volume of 1 cc.). Mechanical mixing in Dr. Brown's emulsifying device was then carried on until a satisfactory emulsion was produced, as judged by microscopic examination. In my experiment 300 back-and-forth movements sufficed.

‖Loveless standard formula that has been used for 14 years.

Note: With the exception of the 1:9:10 preparations, all the emulsions contained 10,000 U./cc. of emulsion.

more active). These data disregard the age of the emulsions.

The responsiveness of the skin to the emulsion chosen for therapy bore a loose connection to the patient's general tolerance toward his treatment, especially if the scratch remained negative. Indeed, there were no adverse reactions of significance under the latter circumstance. When the test proved positive, however, one could not predict whether the individual would show an overdose response. For example, of the 41 patients who exhibited complete tolerance toward their single injection with Tubex-prepared emulsion, 15 reacted to the scratch test utilizing the sample that was shortly to be used for injection. These responses ranged from 1— to 2— in size (a "3" reaction has a wheal of 1 cm. diameter and a surrounding flare of 1.5 to 2 cm.). The reactions to the accompanying scratch test utilizing plain extract of 160 unit strength were always a trifle larger. The 26 other members of this Tubex-treated group gave no response to either test, requiring the 1,280 or 10,240 unit strength of plain extract for any reaction.

The proportion of positive reactors to the scratch test utilizing emulsion was found to be higher when the 16 who gave borderline systemic responses to therapy with Tubex material were examined; that is, there were only three negative results. Furthermore, the positive responses were in general of larger diameter than in the 41 patients who showed complete tolerance to treatment, scratch reactions being as large as 3— in a few individuals. This tendency to react to emulsion was again encountered in the 3 persons who manifested *definite overdose* symptoms. Their responses to the scratch test utilizing the therapeutic emulsions were 1.5, 2—, and 2, respectively, while the wheal-and-flare reactions to 160 unit plain extract were of slightly greater dimension.

From the foregoing relationships, which were confirmed for the other types of emulsion as well, one can conclude that the patient who tolerates about 100 unit strength extract on a scratch (be it exposure to plain extract or to an emulsion that is releasing extract at this rate) will tolerate an injection of that emulsion in the doses prescribed by my eye test classification schedule. For the patient who shows a positive response to the same scratch tests, the probability of overdose reaction to therapy tends to increase as the size of the test reaction increases. In short, the scratch tests serve merely to indicate the level of hypersensitivity. It is the writer's conviction that other types of tests for determining the sensitivity level are superior, notably the conjunctival instillation procedure. The latter, in my hands, has always been more reproducible than the intracutaneous or scarification types. The scratch procedure does, however, have one real advantage over the others; that is, it can be used when one wishes to compare the relative activities of a series of emulsions. Neither of the other tests is suitable for this purpose.

The aforementioned findings make it impossible for me to agree with Dr. Brown that any emulsion capable of eliciting a positive response in an allergic skin by scratch test is a faulty preparation that must be discarded. It would seem more logical to discard the patient, for it is usually not the emulsion that is the variable responsible for the reaction but rather the high order of allergy that exists in the test subject!

Microscopic Determination of Droplet Size: Although each emulsion was examined immediately before it was used for therapy, details of the examination are too abundant to be presented in this article. However, it can be stated that with storage at refrigerator temperature there is a gradual increase in the size and number of droplets that exceed 1μ in diameter. In the case of the Tubex material, for example, perhaps only 1 large droplet could be detected at the outset whereas by the forty-ninth day there were 40 or 50 to be found per high-power field. There was not, however, any obvious tendency for the older specimens to evoke more adverse reactions. It would appear that other factors, notably the degree of allergic sensitivity, play a far more important role in this regard. On the other hand, a more rapid diffusion of aqueous component would be expected to result from a repository that contained numerous large droplets than from one almost uniformly comprised of particles not exceeding 0.8 to 1μ in size, as was the situation with all my emulsions immediately after their initial emulsification. More study is needed to settle this point. Before leaving the topic, I might also say that as coalescence gradually took place, the emulsion showed less tendency to hold its original globularity in water and its initial conical shape when dropped onto a slide. At the same time, there was a reduction in viscidity, detected by extruding some of the emulsion

through a needle. These qualities are more readily demonstrated than are microscopic qualities, which require considerable time in addition to special equipment.

SHELF LIFE OF EMULSIONS AT VARIOUS TEMPERATURES: Emulsions can be characterized by the length of time they retain at a given temperature their original homogeneous, thick (often invertible) "creamy" appearance. In the case of the Tubex preparation, residual emulsion was assigned in a random fashion after therapy to observation at 50° C, 37° C, room temperature, or 6° C. Although most of the latter specimens have thus far failed to show the first signs of water droplet formation, a sufficient proportion of the sample stored at 50° C and in the incubator have separated, permitting a tentative conclusion; namely, breakdown occurred no earlier in emulsions that had evoked overdose reactions than in samples that had caused no adverse developments. As expected, the higher the storage temperature, the quicker the separation of water from the mixtures. End points were reached in 6 to 14 days when emulsion was kept at 50° C, whereas 13 to 25 days were required at 37° C, and 29 to 71 days elapsed before the room temperature storage led to coalescence. None of the Tubex specimens stored at 6° C has as yet exhibited visible droplet development, although more than three months have passed since the earliest shelf tests were started. One must concede, then, that the results of shelf tests thus far offer small promise as an index to the risk of adverse response in a prospective patient.

EYE TEST AS CRITERION

Since the same statement can be made for the microscopic test and to a lesser extent for the scratch test, it seemed indicated to turn back to the eye test as a possible means of predicting the tolerance for injected antigen. Among the group assigned to the Tubex method, I found a crude correlation existing between the degree of conjunctival allergy and the advent of overdose reactions after treatment. As a matter of fact, each of the three definite adverse reactions occurred in individuals whose eyes responded to strengths of only 10, 40, and 80 units respectively. Furthermore, there were borderline manifestations in 6 of the 7 patients whose eye requirements were 20 or 30 units per cubic centimeter. Thus seven eighths of the class A members exhibited at least borderline manifestations of antigen-antibody reaction to their 5,000 unit doses. By way of contrast, 20 of the 29 members of class B showed full tolerance for 7,500 units given in a single injection. The other 9 included, however, the 2 definite reactors mentioned before as having eye requirements of 40 and 80 units per cubic centimeter. Four of the remaining 7 members of class B had requirements of 120 to 240 units, while 3 were more allergic by eye test and required 60 or 80 unit instillations. All 7 exhibited borderline signs of overdosage after therapy. Thus 9 out of 29 members of class B exhibited borderline or more definite adverse signs. The 23 remaining members (class C) of the Tubex-assigned group of 60 were wholly tolerant of their 10,000 unit, single-injection treatments, with the exception of 3 persons. As might have been expected, these fell into the lower levels of the class C conjunctival requirements (480 or 320 units being the end point strengths), and exhibited only borderline adverse reactions.

Hence, the risk of borderline or occasional slight adverse reactions to my recommended dose of emulsion seems distinctly greater as the eye test result is lower, the reaction rates being 87.5 per cent for class A, 31 per cent for class B, and only 13 per cent for class C patients. Obviously, a corrective step would be to reduce the dosage assigned to the class A patient and, for its more allergic members, that now recommended for class B. To attempt to abolish the borderline reactions listed for the rest of group B and for occasional members of class C would be both unnecessary and unwise. This is because the giving of an approximately maximal dose, particularly to a newly acquired patient, affords him the best chance for optimal immunity without undue risk. The physician knows what comprises a maximal dose only after he has induced minor focal reactions in his patient. I have deliberately and rather uniquely sought to do this for many years now.

SUMMARY AND CONCLUSIONS

A modification of my standard water-in-oil emulsion has been evolved that permits the use of two and a half times more aqueous component at the expense of the stabilizing agent, Arlacel A. The resulting 1:6:5 mixture of Arlacel A, Atreol no. 9 mineral oil, and watery allergenic extract still contains 50 per

cent mineral oil. One can now include as many as eight different allergens in a given repository, provided their initial average strength is 192,000 "protein" nitrogen units each. The effective concentration of each, after dilution by the others, will then be 24,000 units per cubic centimeter—the strength needed to provide an emulsion containing 10,000 units per cubic centimeter of emulsion. For a preparation involving only one allergen, the rather low concentration of antigen (24,000 units per cubic centimeter instead of the 60,000 unit material needed in the older 4:6:2 formula) results in a much slower rate of diffusion from the repository into the tissues, since the diffusion rate of solute varies as the square of its concentration.

When the new formula was prepared in one large batch, emulsification could be quickly achieved in a commercial homogenizer. The entire lot was then loaded into sterile cartridges that had been fitted with a 25 gauge needle ready for insertion into a Tubex syringe. These single dose units were then shipped to me by mail and stored at 6° C until used 1 to 48 days later. Some of the batch of ragweed extract made for these emulsions was also available for other emulsion formulas under study, as well as for eye tests (admixed with an equal volume of glycerin to stabilize it). The therapeutic use of Tubex material in 60 ragweed-allergic patients, 29 of whom were new to me, proved it to be well tolerated (5 per cent exhibited mild adverse reactions) despite the fact that full doses of 5,000 to 10,000 units and only one injection (under the skin) were involved. Indeed, the only emulsion to surpass it in safety was my old 4:6:2 formula. By way of contrast, three other emulsions provoked responses of slight or greater intensity in 17 per cent of their recipients. Two of these preparations had been manually mixed and contained my standard materials in the proportion of 1:6:5 or 1:9:10, whereas the third and least well tolerated was a special preparation of a 1:9:10 formula that employed Drakeol rather than Atreol no. 9 as mineral oil and that was mixed for over an hour in Dr. Ethan Allen Brown's mechanical device by Dr. Harold Lecks. For the foregoing experiments a group of 128 patients of unusually high sensitivity (10 per cent belonged in class A, 57 per cent in class B) had been assigned to receive these emulsion formulas in a random fashion, according to eye reactivity.

Thus the new 1:6:5 formula produced and dispensed in a commercial fashion showed a promising degree of safety as a therapeutic agent. The advantages of this single-batch, shippable, ready-to-use product are striking when one considers that my older procedure requires hand emulsification for six minutes of batches that cannot exceed 4 cc. while the mechanical procedures of both Dr. Brown[5] and Dr. Nathan Shaeffer[5] require about an hour's emulsification for similarly small batches. An even greater advantage of the massive production method used by Wyeth Laboratories is that a large supply of uniform emulsion can be had, thus eliminating variables that would inevitably creep into the many small batches prepared by different individuals on different occasions. Furthermore, the risk of error and of contamination during manipulation is removed from the allergist to a specialized, well-equipped commercial laboratory. All these factors are of importance not only from the practical viewpoint but from the theoretical one at this time when intensive exploration of the repository method is taking place.

My attempts to locate criteria for a safe emulsion have been less rewarding. No clear relationship was detected, for example, between the degree of coalescence noted under the microscope and the tolerance exhibited by the recipient of a given emulsion. Dr. Brown[5] asserts that the existence of droplets larger than 0.1 μ renders the emulsion unsafe for human use. Indeed, on the basis of finding larger droplets in one of the Tubex units that came to his hands, he convinced Wyeth Laboratories to recall all they had shipped to my collaborating allergists. My own use, however, of these returns failed to justify his fears.

A second attempt to locate a criterion of safety was no more rewarding. It was comprised of subjecting any emulsion remaining after treatment to shelf-life tests at one of four temperatures. The 50° and 37° C findings to date fail to show that Tubex samples of emulsion were more apt to evoke systemic reactions if they showed early separation of visible water droplets than if a relatively long period of exposure was required for this degree of coalescence. (Heat, of course, catalyzes the inevitable process of separation that occurs in all emulsions.)

The third effort to find a criterion of safety for the Tubex emulsion was the performance of scratch tests with emulsions and with plain

extract in tenfold dilutions. Although there were no adverse responses to Tubex therapy in individuals who showed negative reactions to the scratch test, and although there were positive scratch responses in each of the 3 persons who developed mild but definite adverse manifestations, no such consistent relationships were detected among the numerous other patients who responded to the scratch test. Indeed, many showed full tolerance to injection of the material that had provoked definite wheal-and-flare development on a scratch. This is not surprising, however, since the latter test is merely a conventional skin test carried out with a modified testing solution (the emulsion). It reveals much more about the patient (his degree of sensitivity) than it does about the emulsion. Indeed, I am unable to agree with the contention of Dr. Brown that the capacity of an emulsion to provoke a reaction in the scratch of any patient condemns that emulsion for human use. Although the procedure has limited scope as a criterion of safety, it does serve a useful purpose in comparing the relative release rates of a series of emulsions. In my experience, for example, the 1:9:10 mechanically processed Drakeol emulsion invariably evoked more reaction than any other of the four emulsions. The battery of scratch tests did reveal, therefore, the relative release rates and thereby reflected crudely the relative risk of adverse reaction to the several preparations.

Finally, in view of the established limitations of the skin test, be it carried out by scarification or by endermic injection, as an index to the degree of sensitivity, I examined the eye test results to learn whether they might serve as a better criterion of tolerance to injected emulsion. A definite relationship was now found between the eye's threshold requirement and the patient's subsequent tolerance for injected emulsion—the lower the former, the greater was the risk of adverse reaction to the latter. This led me to conclude that a downward modification of my present dosage schedule should be made for the patients of class A and for the lower half of class B to reduce or eliminate the development of definite manifestations after repository therapy. The borderline reactions, on the other hand, are desirable in that they are the only clear-cut means of showing the allergist that he is giving his patient an approximately "maximal tolerated dose." After all, the latter, especially in the case of a newly acquired patient, holds the greatest promise of conferring optimal clinical immunity—the whole aim of therapy.

As this goes to press, reports from patients are indicating that their relief from hay fever has been comparable to that procured in earlier years, and that the several preparations were equally effective, i.e. 75 per cent responded well.

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Lazy Heart

"Lazy heart," like "television legs" in which the muscles are weak and there is a tendency to thrombosis, is a consequence of modern civilization. It may be that exercising of the arms and legs has become superfluous today in some countries, but even the most persistent sluggard can find himself in situations that place increased demands on his untrained heart muscle. In addition, it is to be expected that if the stress on the heart is constantly below normal, severe degenerative changes will gradually occur. (Raab, W.: Das Faulenzerherz (Die pathogenetische Bedeutung körperlicher Untätigkeit, Wien. klin. Wchnschr. *70:* 709, 1958.)

Electrophoresis of Serum and Ascitic and Pleural Fluids

M. Jeanne Fairweather, M.D.

ELECTROPHORETIC PATTERNS of serum protein have been reported by many investigators since the first descriptions by Tiselius.[1,2] However, in review of the literature relatively few studies are available comparing patterns from normal serum with serum and ascitic and pleural fluids from patients with the diagnosis of cancer or cirrhosis. This paper presents a preliminary report of our studies.

The original purpose of this study was threefold: (1) to set up normal electrophoretic serum patterns and ranges of protein fractions for our laboratory; (2) to determine whether the differences in the protein fractions and electrophoretic patterns were significant enough to warrant using protein electrophoresis of serum and ascitic and pleural fluids as a test in the differential diagnosis of cancer and cirrhosis; and (3) to determine the effect, if any, that therapy with radioactive gold, nitrogen mustard, or phenylalanine mustard might have upon the protein fractions or patterns.

METHODS

Total protein of serum and ascitic and pleural fluids was determined by the biuret method. A modification of the Tiselius technique was used for the electrophoretic separation of proteins. Determinations were performed in duplicate, with both 10 and 20 lambdas of serum and ascitic or pleural fluid applied to separate strips of Whatman filter paper. The strips were supported by horizontal frames. Simultaneous determinations of serum and ascitic and/or pleural fluids were run on samples that had been collected at the same time. Staining was done by bromphenol blue. The Analytrol was used for fraction interpretation. Ranges are reported as a percentage of the total. Values for each group were calculated for range, mean, and standard deviation.

Dr. Fairweather was a Fellow in Medicine, University of Texas, M. D. Anderson Hospital and Tumor Institute, Houston, at the time this research project was conducted. She is presently at Brooke Army Hospital, Fort Sam Houston, Texas.

MATERIAL

During the seven months of this investigation all patients selected for this report were seen by us and in all instances the clinical diagnosis was verified. Unfortunately, it was possible to obtain pretherapy and posttherapy specimens from only a few patients for the following reasons: (1) specimens were lost, (2) some patients did not reaccumulate fluid, (3) some died before further studies could be obtained, (4) further "taps" were not considered advisable for some patients, or (5) specimens were not obtained at the proper times. Therefore, many patients were dropped from the study. To be reported here are data on 22 normal persons, 2 cirrhotic patients, and 47 patients having the diagnosis of cancer. The types of malignant growths were as follows: carcinoma of the breast, 12; carcinoma of the lung, 7; carcinoma of stomach and colon, 5; carcinoma of the ovary, 4; Hodgkin's disease, lymphosarcoma, hepatoma, leukemia, and adenocarcinoma of the endometrium, 3; and lymphoma, melanoma, cancer of the thyroid, and fibrosarcoma, 1.

RESULTS

Serum. For this study blood was obtained from 22 normal active adults between the ages of 22 and 45 years. These were blood donors and laboratory technicians in good health. Each was questioned concerning present illness, allergy, or past illness that might affect the serum pattern (table I, Fig. 1*A*). Jencks,

TABLE I
Serum of Twenty-Two Normal Adults

	Range	Mean	S.D.
Albumin, %	39-51	45.6	3.2
Alpha$_1$, %	4-8	6.1	1.1
Alpha$_2$, %	9-16	12.0	1.8
Beta, %	12-22	17.0	2.7
Gamma, %	12-26	19.0	3.3
Total Protein, %	6.4-8	6.8	1.3

TABLE II
Serum of Two Cirrhotic Patients

	Range	Mean	S.D.
Albumin, %	21-24	22.5	6.4
Alpha$_1$, %	6-8	7.0	1.9
Alpha$_2$, %	8-10	9.0	4.3
Beta, %	14-17	15.0	3.1
Gamma, %	41-51	46.0	7.6
Total Protein, %	4.4-6.8	5.6	--

Smith, and Durrum [3] showed no significant change in serum protein because of age or sex difference.

Only 2 cirrhotic patients were available for study. The ranges obtained are recorded in table II while the characteristic pattern is shown in figure 1*B*.

Pretherapy serum was drawn from 47 patients varying from 19 to 72 years of age with the diagnosis of cancer (table III, Fig. 1*C*).

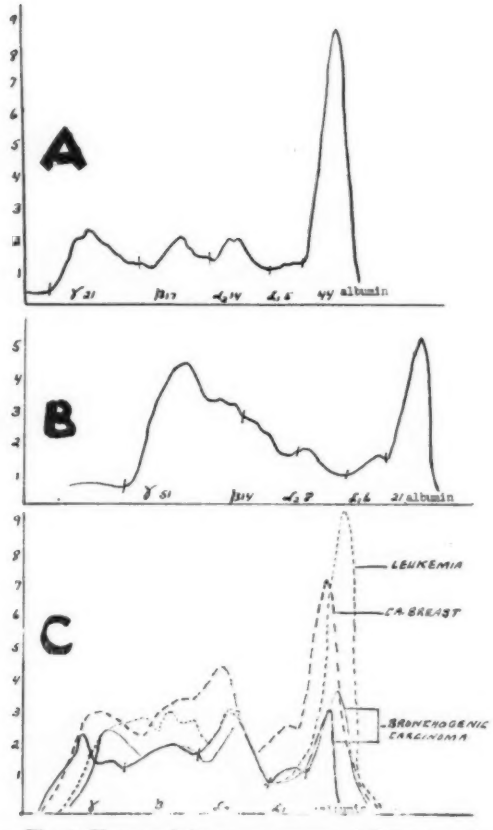

Fig. 1. Characteristic serum patterns. (*A*) In normal patients. (*B*) In cirrhotic patients. (*C*) In patients with cancer.

Thirty-six posttherapy serum samples were obtained from 27 patients (table IV) receiving the following types of therapy: nitrogen mustard (HN_2) intravenously, 4, intrapleurally, 1, and intraperitoneally, 2; thio-tepa intravenously, 3, and intrapleurally, 2; radioactive gold (Au^{198}) intrapleurally, 4, and intraperitoneally, 5; phenylalanine mustard (PAM) intravenously, 2; prednisone (Meticorten) intravenously, 2; chlorambucil (Leukeran) intravenously, 1; and 5-fluorouracil intravenously,

TABLE III
Pretherapy Serum of Forty-Seven Patients with Cancer

	Range	Mean	S.D.
Albumin, %	12-42	28.7	6.4
Alpha$_1$, %	5-13	7.9	1.9
Alpha$_2$, %	8-25	16.9	4.3
Beta, %	13-26	19.9	3.1
Gamma, %	14-45	26.4	7.6
Total Protein, %	4.4-8.5	6.3	1.1

1. Sixteen of the 47 patients mentioned in this series received no chemotherapy. Unfortunately posttherapy specimens from the remaining 4 were lost.

Ascitic Fluid. Nineteen of the 47 patients with cancer had ascites; however, only 15 had pretherapy paracenteses, and only 11 posttherapy specimens were obtained (table V, Fig. 2*A*). The percentage changes in the fractions of ascitic fluid and serum after therapy with HN_2 intraperitoneally and PAM intravenously

TABLE IV
Thirty-six Samples of Posttreatment Serum from Cancer Patients

	Range	Mean	S.D.
Albumin, %	12-47	31.7	7.8
Alpha$_1$, %	5-13	7.9	1.7
Alpha$_2$, %	9-27	16.9	4.6
Beta, %	15-27	20.7	2.8
Gamma, %	14-39	22.8	5.4
Total Protein, %	4.3-8.5	6.4	1.0

TABLE V

Ascitic Fluid from Patients with Cancer

	Pretherapy Fluid, 15 Specimens						Posttherapy Fluid, 11 Specimens					
	10 Lambdas			20 Lambdas			10 Lambdas			20 Lambdas		
	Range	Mean	S.D.	Range	Mean	S.D.	Range	Mean	S.D.	Range	Mean	S.D.
Albumin, %	21-42	31.8	6.7	24-44	34.2	6.1	28-36	32.3	4.0	23-42	32.7	5.7
Alpha$_1$, %	7-14	10.5	2.2	5-14	9.1	2.7	9-14	10.7	2.9	6-12	9.3	2.1
Alpha$_2$, %	9-13	10.8	1.3	8-14	10.6	1.9	10-12	10.7	1.2	7-15	11.0	2.8
Beta, %	14-35	19.5	6.1	13-22	17.4	3.2	16-18	17.0	1.0	12-25	16.5	3.8
Gamma, %	12-38	27.4	8.2	20-38	28.9	5.8	27-32	29.3	2.5	24-46	30.5	6.0
Total protein, %	1.7-5.9	3.3	1.3	1.7-5.9	3.3	1.3	3.0-5.0	4.1	0.6	3.0-5.0	3.8	4.1

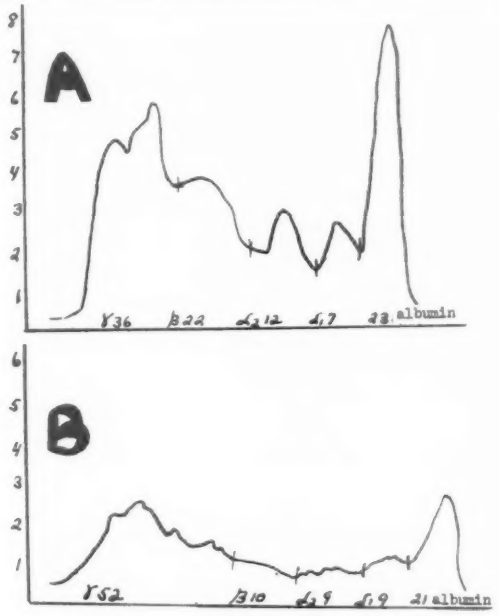

Fig. 2. Ascitic fluid. (*A*) In typical carcinomatosis. (*B*) In typical cirrhosis.

are demonstrated in table VI, where it may be noted that in the ascitic fluid of these patients the percentage of albumin dropped while the percentage of gamma globulin rose after chemotherapy; after PAM was given intravenously the percentage of albumin in the serum dropped whereas the percentage of alpha$_1$ and beta globulin rose. The percentage of alpha$_2$ and gamma globulin also rose but less than the other fractions. After therapy with HN_2 intraperitoneally the percentage of albumin in the serum rose but the percentage of alpha$_1$ and alpha$_2$ dropped slightly. This is, of course, too small a group to permit any conclusions.

Ascitic fluid was obtained from the 2 cirrhotic patients. The albumin and protein fractions are shown to be similar in both serum

TABLE VII

Ascitic Fluid and Serum from Two Cirrhotic Patients

	Case 1		Case 2	
	Ascitic Fluid	Serum	Ascitic Fluid*	Serum
Albumin, %	22	21	—	24
Alpha$_1$, %	9	6	—	8
Alpha$_2$, %	8	8	—	10
Beta, %	10	14	—	17
Gamma, %	51	51	—	41
Total protein, %	lost	4.4	0.7	6.8

* Too low to measure.

TABLE VI

Ascitic Fluid and Serum Before and After Chemotherapy in Patients With Cancer

	Ascitic Fluid				Serum			
	Pre-PAM I.V.	Post-PAM I.V.	Pre-HN_2 Intra-abdominally	Post-HN_2 Intra-abdominally	Pre-PAM I.V.	Post-PAM I.V.	Pre-HN_2 Intra-abdominally	Post-HN_2 Intra-abdominally
Albumin, %	37	30	44	32	38	23	22	28
Alpha$_1$, %	10	11	9	12	5	10	12	9
Alpha$_2$, %	14	13	11	8	15	18	19	17
Beta, %	16	17	13	14	21	26	20	19
Gamma, %	23	29	23	34	21	23	27	27
Total protein, %	4.8	4.0	3.0	3.4	6.8	6.2	5.1	5.3

TABLE VIII
Pleural Fluid from Patients with Cancer

	Pretherapy Fluid, 24 Specimens						Posttherapy Fluid, 28 Specimens					
	10 Lambdas			20 Lambdas			10 Lambdas			20 Lambdas		
	Range	Mean	S.D.	Range	Mean	S.D.	Range	Mean	S.D.	Range	Mean	S.D.
Albumin, %	19-54	37.5	7.6	11-48	37.5	9.8	28-58	40.2	2.6	33-54	41.5	6.7
Alpha$_1$, %	6-12	8.7	2.1	5-15	8.0	2.5	6-13	9.2	2.1	4-9	7.1	1.3
Alpha$_2$, %	6-17	10.8	2.6	8-19	11.3	3.2	6-17	10.8	3.4	4-17	11.1	3.2
Beta, %	12-21	15.7	2.0	11-29	18.0	3.9	14-21	16.8	2.4	12-20	16.5	2.5
Gamma, %	20-40	27.5	5.6	16-42	25.3	6.7	13-29	22.9	4.5	17-28	23.8	3.5
Total protein, %	1.0-6.2	4.1	1.1	1.0-6.2	4.1	1.1	2.6-5.1	4.2	0.8	2.6-5.1	4.2	0.8

and ascitic fluid (table VII). The electrophoretic patterns of serum and ascitic fluid may be compared by referring to figures 1*B* and 2*B*.

Pleural Fluid. Twenty-four pleural fluid specimens were obtained from patients with cancer before therapy was instituted. Twenty-eight specimens were obtained from 24 patients after therapy (table VIII). Figure 3 compares serum and pleural fluid patterns of the same patient one day before and two days after therapy with Au^{198} intrapleurally.

DISCUSSION

A marked difference in comparison of the protein and albumin fractions in the serum of normal, cirrhotic, and cancerous individuals can be seen by comparing tables I, II, and III. There is considerable overlapping of the ranges but there are characteristic differences. The cirrhotic patient has a lower mean of the albumin, alpha$_2$, and beta globulins but a much higher gamma globulin fraction than either the normal or the cancerous patients. The normal patient's serum contains a much higher amount of albumin than does serum from patients with cancer. Percentages of alpha$_2$ and beta globulin are at their highest in cancer. The presence of a large area of tissue destruction is closely associated with an in-

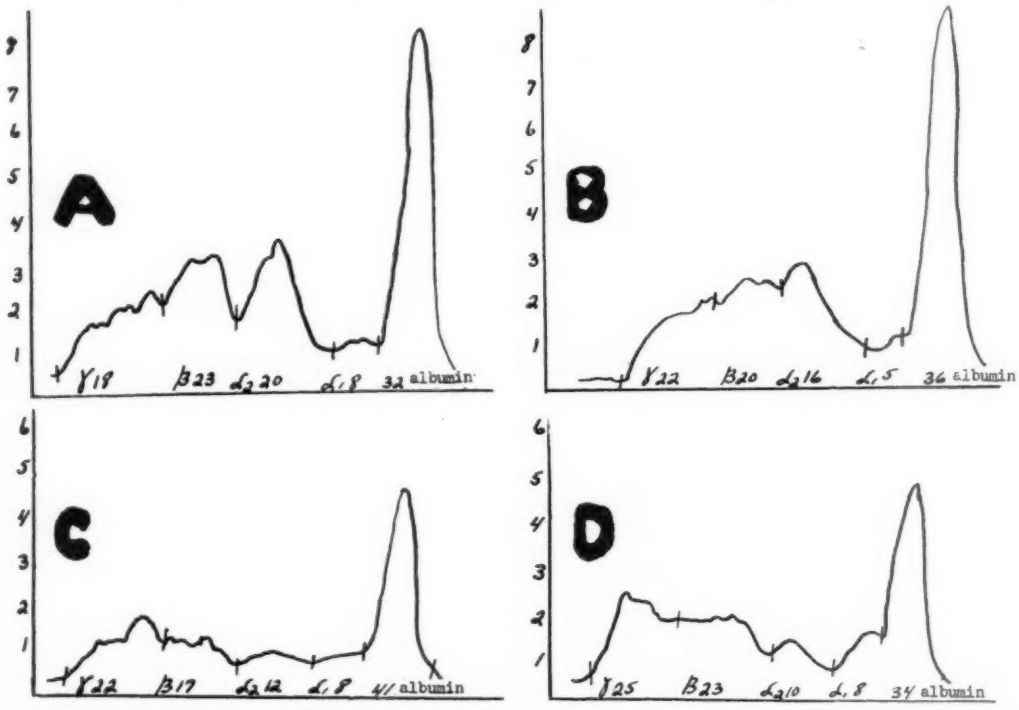

Fig. 3. Pleural fluid and serum before and after therapy with Au^{198} intrapleurally. (*A*) Serum one day before therapy. (*B*) Serum two days after therapy. (*C*) Fluid one day before therapy. (*D*) Fluid two days after therapy.

crease in both alpha globulin bands. The percentage of gamma globulin is at its lowest in normal patients.

The appearance of the actual patterns is of great diagnostic aid, as can be seen by referring again to the characteristic tracings (Fig. 1). DeWael [4] emphasized that cases of cirrhosis of the liver may be distinguished from tumor by large and characteristic beta and gamma globulin bands. Spak [5] felt that the small bands of alpha$_1$ and alpha$_2$ globulin were even more characteristic.

Spak [5] reported that the total protein level in the ascitic fluid of his patients with cancer ranged from 2.5 to 6 Gm., with a mean of 4.2. In the present study the total protein level for this group ranges from 1.7 to 5.9 Gm., with a mean of 3.3. To compare ranges of protein fractions in cirrhotic and malignant ascites, see tables V and VII. The percentages of albumin and beta globulin fractions and the total protein level are much lower in the former. The percentage of gamma globulin is, however, considerably higher in the cirrhotic fluid.

Macheboeuf and coworkers [6] concluded that the electrophoretic pattern was the same in ascitic fluid as in serum. Spak [5] found that the amount of albumin in practically every case was higher in ascitic fluid than in serum. In the majority of our patients with cancer this was confirmed.

No pleural fluid from the 2 cirrhotic patients was available for study. In patients with cancer the amount of albumin is higher in pleural fluid than in serum (tables III and VIII). The alpha$_2$ and beta globulin fractions and the total protein level are lower in the pleural fluid.

Two very unusual patterns have appeared in our study which deserve mention. Figure *4A* shows the electrophoretic pattern of serum from a patient with the diagnosis of reticulum cell sarcoma. These fractions are not included in the preceding tables, as the report arrived after all calculations had been made. The gamma globulin fraction of 59 far exceeds the highest in our normal patients (26) and the highest in our cancerous patients (45). All other fractions are much lower than in the normal patients, especially albumin and beta globulin. The sharp peak of the gamma fraction with the shoulder differs markedly from the gamma peak seen in cirrhosis (Fig. *1B*) or myeloma (Fig. *4B*). The moving boundary electrophoresis of this serum shows

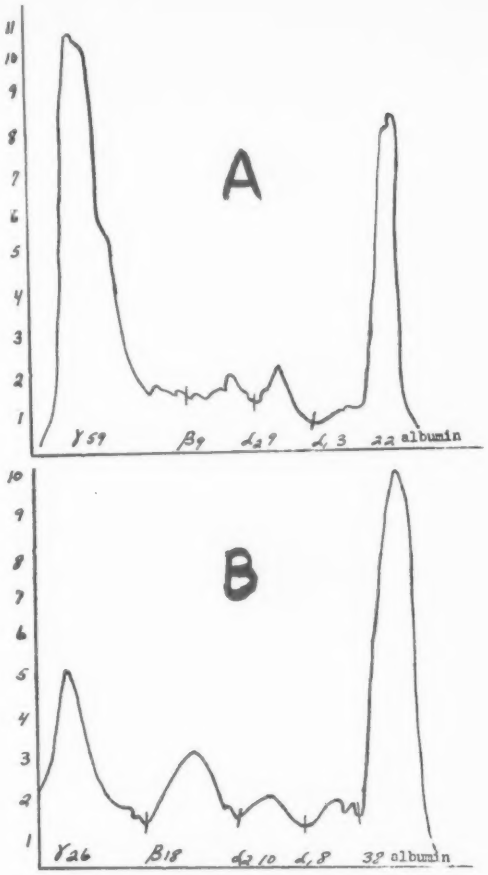

Fig. 4. Serum in 2 patients with cancer. (*A*) In reticulum cell sarcoma. (*B*) In typical multiple myeloma.

an enormously high, sharp spike representing this gamma globulin fraction.

The serum and pleural fluid patterns of a patient with carcinoma of the breast, with metastases, are seen in figure *5A* and *C*. There is a very high abnormal peak of the beta globulin fraction in the serum which is not prominent in the pleural fluid. Figure *5B* and *D* shows the marked change in patterns six months later. In the interval a hypophysectomy had been performed. The abnormal percentage of beta globulin had disappeared from the serum, but there is now a high-peaked abnormal alpha$_2$ fraction. The percentage of gamma globulin has decreased considerably in the pleural fluid pattern.

SUMMARY AND CONCLUSION

Ranges for total protein, albumin and globulin fractions of serum, and ascitic and

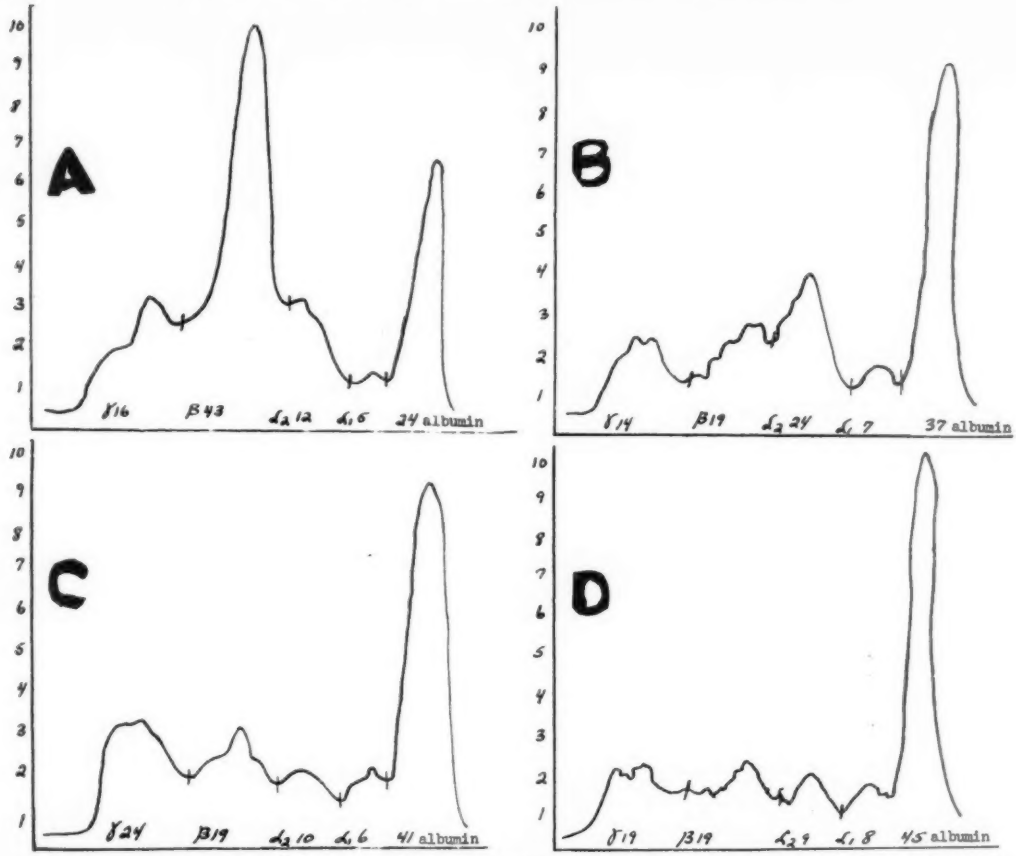

Fig. 5. Serum and pleural fluid in patient with breast carcinoma. (*A*) Serum before therapy. (*B*) Serum after hypophysectomy. (*C*) Pleural fluid before therapy. (*D*) Pleural fluid after hypophysectomy.

pleural fluids have been presented for normal, cirrhotic, and cancerous patients in our study. Typical electrophoretic patterns have been shown. Studies before and after therapy, including two unusual patterns, have been discussed.

Although this series is small, it is concluded that protein electrophoresis of serum and ascitic and pleural fluids is a valuable guide in differential diagnosis of effusion due to cirrhosis and cancer. Further study is recommended.

ACKNOWLEDGMENT

The author wishes to acknowledge the excellent aid of Frank H. Connell, M.D., Chief of Section of Clinical Pathology, Department of Pathology; Suzanne Beerstecher, research assistant; and James Pokluda and Allen Bartlett, laboratory technicians, University of Texas, M.D. Anderson Hospital and Tumor Institute, Houston, Texas.

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Summary of Three Years' Clinical Experience with a New Form of Ferrous Sulfate

Mary P. Sterling, M.D.

IRON DEFICIENCY ANEMIA, commonest of all anemias and probably the commonest single clinical entity in women, is truly one of medicine's "stepchildren." Its symptoms are rarely severe enough to prompt a patient to seek medical advice, and its treatment, while producing improvement that the patient seldom recognizes, frequently causes discomfort more obvious and annoying than the disorder itself. Because of these factors, iron deficiency anemia frequently goes untreated or, at best, is treated inadequately, tending to recur or become chronic.

In searching for a clinically suitable form of iron therapy, I have appraised most of the currently available iron salts and their various dosage forms. I have found that efficacy is not an important consideration, since practically any iron salt is capable of reversing iron deficiency anemia, provided the patient is able to tolerate it in therapeutic doses. This latter point of patient tolerance, however, is frequently a problem, and finding a preparation that at therapeutically effective doses produces a minimum of side effects in the average patient can be difficult.

This report presents a summary of my three years of clinical experience with a new sustained-release dosage form of ferrous sulfate (Feosol Spansule) in capsule form, which substantiates the observations[1,2] that small, frequently administered doses of iron are capable of producing adequate hematopoietic responses with a minimum of annoying side effects. To achieve the effect of frequent administration, the iron content of each capsule is divided among a great many small pellets, designed to disintegrate at varying rates after ingestion. Because of their special coatings, virtually all the pellets pass intact through the stomach and are dispersed throughout the small intestine where, after their disintegration, the iron is absorbed. During the past three years, I have found that one capsule a day is capable of producing a hematopoietic response in most patients that is equivalent to that of preparations containing roughly three times as much elemental iron. To illustrate these results, I have randomly selected 60 case histories that typify the responses obtained in approximately 400 patients.

Dr. Sterling is Medical Staff Physician and Courtesy Staff Physician in Obstetrics, Presbyterian Hospital, and Medical Staff Physician, Women's Hospital, Philadelphia.

DATA ON PATIENTS

The patients' ages, pretherapy hemoglobin levels, and duration of therapy are shown in table I. As will be noted, 7 of the obstetric patients had initial hemoglobin levels that were below normal, averaging 10.4 Gm. per 100 cc. All the nonpregnant patients initially had abnormally low hemoglobin levels, averaging 9.6 Gm. per 100 cc., that were secondary to disorders such as menorrhagia, peptic ulcer, arthritis, carcinoma, cirrhosis, and dietary deficiencies, or were the result of radiation or drug therapy. Thirty-nine of the 60 patients had previously received one or more of the standard iron preparations. Hematopoietic response to these previous medicaments was usually adequate, although 10 (50

TABLE I

Summary of Results of Treatment with Sustained-Release Ferrous Sulfate

Patient Category	No. of Patients	Age, Yr.		Hg., Gm./100 cc.					Duration of Therapy, Wk.	
				Pretreatment		Posttreatment		Change		
		Average	Range	Average	Range	Average	Range		Average	Range
Pregnant										
Normal	13	26.3	20-41	13.3	12-14.5	13.9	13-15.5	+0.6	28.0	12-36
Anemic	7	29.0	22-43	10.4	10-11	13.4	12.8-13.8	+3.0	25.1	16-32
Nonpregnant										
Premenopausal	20	37.0	24-45	9.3	5.4-10.5	13.8	13-14.5	+4.6	10.5	8-18
Postmenopausal	20	66.6	45-82	10.0	8-11	13.7	12.5-15.5	+3.7	12.0	4-20

per cent) of the pregnant and 29 (72.5 per cent) of the nonpregnant patients had experienced side effects. In 17 patients side effects were severe enough to warrant discontinuation of therapy.

TREATMENT

All patients were examined and blood and urine specimens were collected. Additional studies such as sedimentation rate, roentgenography, gastric analysis, and electrocardiography; blood urea nitrogen, phenolsulfonphthalein, blood sugar, and serum cholesterol levels; and the icteric index were done as required. In addition to specific medicaments or therapy, all nonpregnant patients were instructed to take one capsule of the iron preparation daily. Obstetric patients were placed on therapy once pregnancy was confirmed, 13 receiving the preparation as a prophylactic measure and 7 for therapeutic purposes.

RESULTS

Although patient tolerance is the major concern of this report, changes in the hemoglobin level are also presented in table I as evidence that the reduced incidence and severity of side effects were not obtained at the cost of adequate therapeutic effects.

Pregnant Patients. Obstetric patients whose hemoglobin levels were normal initially exhibited small average increases; the 7 anemic patients in the group experienced an average increase of 3 Gm. per 100 cc. At delivery, all the patients had a hemoglobin level of at least 12.8 Gm. per 100 cc., and most had levels of 13.5 Gm. per 100 cc. or above. Hemoglobin levels in the 11 patients who returned for post-partum checkups (approximately half of whom were anemic at the start of therapy) were consistently above 13 Gm. per 100 cc., indicating that any deficit incurred by blood loss at delivery and in the puerperium was rapidly compensated for by the medicament.

Table II shows the type and severity of side effects that were reported by the pregnant patients during previous and present therapy. Ten of the 20 patients reported a total of 20 side effects, averaging 2 per patient: 8 of these were mild, 10 moderately severe, and 2 severe. Five of the patients experiencing side effects had to discontinue iron therapy. During therapy with the sustained-release preparation, 3 patients reported a total of four side effects—all four being mild.

Nonpregnant Patients. Initial hemoglobin levels were generally lower in the premenopausal than in the postmenopausal patients

TABLE II

Incidence and Severtiy of Side Effects Due to Iron Therapy—Reported by Pregnant Patients

Side Effect	Previous Iron Therapy			Sustained-Release Iron Capsules		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Epigastric distress	5	1	0	1	0	0
Nausea	2	2	0	1	0	0
Anorexia	0	0	0	0	0	0
Diarrhea	0	2	0	0	0	0
Constipation	1	5	2	2	0	0
Total	8	10	2	4	0	0

TABLE III

Incidence and Severity of Side Effects Due to Iron Therapy—Reported by Nonpregnant Patients

Side Effect	Previous Iron Therapy			Sustained-Release Iron Capsules		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Epigastric distress	5	9	6	3	0	0
Nausea	4	4	0	1	0	0
Anorexia	1	1	0	0	0	0
Diarrhea	1	4	1	1	1	0
Constipation	4	14	12	12	1	0
Total	15	32	19	17	2	0

and, as would be expected, the response of the former group to therapy was slightly greater, averaging an increase of 4.6 Gm. per 100 cc. as against an increase of 3.7 Gm. per 100 cc. in the postmenopausal patients. As would also be expected, increases in hemoglobin levels during therapy were generally smaller and more gradual in patients whose primary condition or concomitant therapy causing the anemia had remained unchanged. When the patients in these two groups discontinued therapy, all hemoglobin levels were within normal limits and ranged from 12.5 to 15.5 Gm. per 100 cc.

Table III shows the type and severity of side effects that were reported by the nonpregnant patients during previous and present therapy. Twenty-nine of the 40 patients reported a total of 66 side effects, averaging 2.3 per patient: 15 of these were mild, 32 moderately severe, and 19 severe. Twelve (41 per cent) of these 29 had to stop iron therapy because of side effects. During therapy with the sustained-release preparation, 18 patients, all of whom had experienced side effects with previous iron therapy, reported a total of 19 side effects, averaging 1 per patient. Of these side effects, 17 were mild and 2 were moderately severe; no severe side effects were reported. Since the side effects occurred almost entirely in the large intestine, one could conclude that the pellets disintegrate in the small intestine and in the stomach.

SUMMARY AND CONCLUSIONS

The clinical evaluation of a three year study of a sustained release oral iron preparation (Feosol Spansule) in 60 female patients showed side effects to be consistently milder and less frequent than with previously used iron medicaments. Withdrawal was not necessary in any case. The rise in hemoglobin level was satisfactory in all patients. This preparation should be of particular value for individuals who cannot tolerate conventional oral iron preparations, especially when prolonged therapy is necessary.

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Figures on Diabetes in the United States

Diabetes mellitus, the eighth leading cause of death in this country, afflicts 1 out of every 80 Americans, according to the publication "Patterns of Disease." There are a million diabetic individuals and as many persons with undiagnosed cases of the disease. In addition, 4,750,000 persons are potentially diabetic, and each year 65,000 persons in the United States become diabetic. Also, one person in four in the population is a carrier, who transmits to offspring the tendency toward diabetes.

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Anorexia	1	1	0	0	0	0
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The Place of Research in the Nutrition Work of WHO

From the Nutrition Section, WHO Headquarters, Geneva, Switzerland

UNDERNOURISHMENT AND MALNUTRITION are, jointly or separately, directly or indirectly responsible for much of the world's ill-health. In attacking the problem the World Health Organization collaborates closely with the Food and Agricultural Organization, WHO being primarily concerned with nutrition as it affects public health and FAO with raising standards of living and levels of nutrition and with improving the production and distribution of all food and agricultural products. Both organizations serve their member countries by providing direct technical assistance when requested by the government concerned, and by stimulating, supporting, and co-ordinating the various investigations necessary to ensure a sound basis for any action.

In many countries combinations of communicable disease and malnutrition exist and are responsible for high mortality and morbidity rates in the younger age groups and for poor health and low productivity in the adult population. More effective control of the intercurrent infections and infestations has, in recent years, made it possible to see the full significance of malnutrition as a public health problem. Moreover, the increases of population brought about by the more effective control and treatment of certain diseases previously responsible for many deaths have emphasized the urgent need to increase and improve food supplies if a widespread lowering of the general public health through undernourishment and malnutrition is to be avoided.

The infant mortality rate has long been considered an index of the general level of public health and development in any region. More recently, it has been recognized that in some countries the mortality rate in the group aged 1 to 4 years is perhaps a more sensitive index of the extent of the environmental hazards that concern the public health worker. Where the infant mortality rates are 5 to 10 times higher than those in the economically developed countries, the mortality rates in the 1 to 4 year age group are often 10 to 20[1,2] times higher than the corresponding rates in the wealthy countries. The evidence suggests that nutritional factors may play a large part in the creation of these high rates in this age group.[3] Governments of many countries have sought WHO's help in their efforts to reduce deaths and ill-health among children, and WHO's task has been, in the main, one of collecting and scrutinizing the evidence, seeking measures that seem likely to lead to a reduction in the nutritional component of the total mortality, and assisting governments to devise the means of putting these measures into operation.

The two main causes of nutritional ill-health —lack of enough food and lack of the right kind of food—often occur together and, as stated above, are generally further complicated by the debilitating infections and infestations that abound where standards of living and environmental hygiene are low. In such populations the infant after weaning has no other food available to him than those parts of the adult diet that he can eat and digest. His immaturity requires omissions from the total diet, which results in his over-all nutrition being grossly inadequate and ill-balanced. Often too, the quality of the total diet is unsuitable for the maintenance of health, especially the health of the vulnerable groups—pregnant and lactating women and young children. In these circumstances deficiency diseases such as beriberi, pellagra, anemia, avitaminosis due to lack of vitamin A, and the protein deficiency syndrome most commonly known as kwashiorkor are to be found.

Much can be done even within existing economic circumstances to improve the health of these large populations, but general measures are not usually applicable because the nature of the problem varies in different countries and even in different areas within the same

country. Quite apart from the quality and quantity of the diet there is the matter of the prevalence of conditions such as dysentery and intestinal helminthiasis, which affect the picture considerably. It is obvious that much research and many and varied investigations have to be carried out before the nutritional problem can be adequately defined and means for its relief devised and made to work effectively.

Until recently, WHO has not conducted extensive research; it has, however, drawn on the skills and experience of recognized experts in various fields through expert committees convened from time to time, through specially organized meetings of scientists concerned with different aspects of a nutritional problem, by giving financial support to research work in progress in different countries, or by supplying consultants to countries that wish some particular investigation to be carried out. A brief description of the work carried out during the past few years on one of the most important and widespread nutritional public health problems will illustrate the ways in which these means can be effective in combating malnutrition.

Kwashiorkor, associated with an insufficient intake of protein, occurs essentially at the weaning and postweaning periods. It may be due to a total deficiency of protein or to an imbalance of amino acids; it is only in recent years that the condition has been recognized. Surveys to establish its prevalence have been carried out by WHO and FAO in Africa,[4] Central America,[5] and in Brazil.[6] These, together with national surveys carried out in India[7] and other countries, have shown that kwashiorkor, although known by different names, is a widespread nutritional disorder and a major problem in many areas. The underlying causes are numerous: low productivity of the land and the effects of general poverty and inability to produce suitable foods in the area or failure to adopt suitable methods for food processing and preserving. Traditional customs, such as that of reserving the scarce morsels of meat for the aged or the wage earner, or even ignorance, may lead to failure to recognize and use existing resources. The prevention of protein malnutrition, therefore, often requires some fundamental changes in the way of life of the people and may entail a co-operative effort on the part of the health, agriculture, economic, fisheries, and education departments of the countries concerned.

WHO and FAO have stimulated interest and research in this problem in a number of different ways. In West Africa in 1952 a meeting was arranged that brought together workers in nutrition from a wide geographical area. This undoubtedly played an important part in the recognition that kwashiorkor is fundamentally the same problem throughout the world, even though it may vary a little in its clinical manifestation from area to area.

A great deal of research is going on in different centers, much of it devoted to discovering ways of feeding children satisfactorily without using the animal-protein-rich foods, such as milk and eggs, which are sometimes unobtainable and almost always expensive. In 1953 WHO and FAO, with the financial assistance provided by the Josiah Macy, Jr. Foundation, were able to bring together in Jamaica workers engaged in research on the various aspects of kwashiorkor in different parts of the world. The value of this meeting has been amply demonstrated by its influence on the lines that research followed in different centers and the results of these efforts.

Where protein malnutrition is caused by the inability of the people to obtain a suitable protein-rich food, the solution must lie in finding a cheap source of such food. In recent years WHO has made grants to three research centers (in East Africa, Guatemala, and South India) to assist them in investigating the suitability of vegetable protein from different sources for the prevention of protein malnutrition, and also arranged an exchange of workers between these centers, which has led to valuable co-ordination in their research work.

A further grant from the Josiah Macy, Jr. Foundation enabled a second conference to be held on protein in nutrition. This time the emphasis was on the practical methods of dealing with protein deficiency—especially in the diet of young children. Some foodstuffs, which in their natural state are not suitable for a young child, may be made so by processing or combining them with other foods. Much has to be known before such preparations can be developed and careful preliminary testing is essential before their use for child feeding on a large scale can be advocated. Agreement was reached among experts in protein nutrition, biochemists engaged in the experimental feeding of animals, scientists studying the most efficient methods of stock feeding, pediatricians, and general medical nutri-

tionists as to how the necessary trials should be conducted.

The final decision as to the safety and suitability of any food is a highly specialized matter, and a "protein advisory group" comprised of experts was established to review progress in research from time to time. In addition to giving technical advice, the members of this group assist also by conducting in their own laboratories and wards tests of different foodstuffs or by suggesting other institutes competent to do so.

The work being done by the international bodies on this problem has aroused wide interest, and the Rockefeller Foundation has donated $550,000 to encourage research on the development of new protein-rich foods. This money is being used as grants to various workers throughout the world. This program is carried out jointly with FAO and the United Nations Children's Fund (UNICEF), and the latter has provided substantial financial support for it.

The other main approach in the prevention and alleviation of protein malnutrition (and other forms of malnutrition) is education of the people in the use of newly introduced foods and/or better use of those already available. When we inquire into the reasons for the all too frequent disregard of local foods, we soon find ourselves in the baffling maze of ignorance, tradition, taboo, and magic, and of the whole system of belief of the people about health and disease. In the past most nutrition and health workers have tried, by repeated blows of didactic teaching, to hammer their way through this maze and break down the resistances to unaccustomed foods and eating practices—with very little success. Sometimes an isolated change has produced unforeseen and undesired results. Under Western influence in some countries, the practice of prolonged breast feeding has declined and the child now faces the hazards of weaning with a much less mature digestive capacity. It is thought that this may have greatly increased the incidence of kwashiorkor.[8] In order to avoid such mistakes in the future, public health workers have turned to the anthropologist whose knowledge of the social structure and habitual practices of a community can help us to predict, to some extent, the effects of changes in these practices. Not nearly enough is known and recorded, however, about the food habits and the beliefs on health and disease in the countries where protein malnutrition occurs, and WHO is trying to fill in some of the blanks and to encourage others to do so. A survey of the infant-feeding practices and nutritional diseases in the tropics was carried out in 1953 by a consultant; a publication followed this investigation sponsored by WHO.[9]

Studies have also been made in Indonesia and Guatemala of the food practices and influences that govern these practices, and of other social and cultural factors associated with protein malnutrition and other forms of malnutrition in children. Information was sought on such things as: attitudes toward mortality in children; the relationship between family instability and sickness, especially malnutrition; the influence on nutritional status of adoption and of differences in attitudes toward male and female children; and clan structure and social mobility in their relation to food and patterns of consumption. These studies have provided much information on the causes of malnutrition in these countries and have shown that the problem of malnutrition in children cannot be solved by purely technical measures. It is hoped that they will be useful guides to nutrition workers elsewhere.

The psychological importance of certain foods and feeding practices and the resistances aroused by attempts to change related habits have so far aroused little interest among nutrition workers. More and more attention is, however, being given to the underlying motives that govern our actions and choices in this field. The third meeting in the protein malnutrition series, largely financed by the Josiah Macy, Jr. Foundation and sponsored by a number of international bodies, took place in September, 1960, to consider the psychological and cultural blocks to better nutritional practices in certain communities and how best they may be overcome.

Another field in which the results of an increasing volume of research work have been used by WHO and FAO is that of nutrition education. It is now recognized that routine nutritional advice based on scientific principles is not enough, and that if people are to be persuaded to change long-established habits much more active methods must be employed. By means of international seminars held in different parts of the world, WHO and FAO are trying to raise the standards of health and nutrition education among field workers, physicians, nurses, teachers, and others. Other four

to five month courses have also been organized, to ensure that the scientific facts of nutritional health and disease, on which all education and practice must be based, are thoroughly understood by those responsible for carrying out the work in different countries.

The same general principles of studying the problem on the ground, devising means for its solution and helping governments to implement the necessary measures, have been followed in connection with other nutritional problems; for example, endemic goiter, pellagra, eye diseases, beriberi, and more recently the degenerative heart diseases. In this work WHO has been content to use, support, and co-ordinate the relevant research work being carried out in different parts of the world. Now, however, consideration is being given to the ways and means whereby WHO might use its unique facilities more actively in the research field.

The possibilities in the field of nutrition are numerous, and, when one remembers that malnutrition occurs mostly in countries that have not yet fully developed adequate facilities for conducting their own investigations, it appears that this field is particularly suitable for international work.

In certain countries diarrheal diseases kill more young children than do all other diseases combined. The nutritional condition of the child is of considerable importance in both the onset and outcome of the disease. Comprehensive epidemiologic studies have already been begun with the help of WHO in several regions. The relationship between parasitic intestinal infections and the nutritional state is not yet fully established. Preliminary surveys carried out in certain areas on the etiology of the iron deficiency anemias will, it is hoped, help to clarify this relationship and enable further action on a sound basis. Similarly, the relationship between nutritional status and bilharzic infection seems to be important in determining the individual's tolerance of this infection and his degree of invalidism. Here again, epidemiologic studies are needed to define the exact role nutrition plays in this disabling disease.

The recent increase in the incidence of the degenerative heart diseases has aroused much concern. Intensified research in the biochemical and epidemiologic aspects of these diseases during the past 10 years has shown that habitual diet plays an important part in the development of these conditions. A study group,[10] convened in 1955, reviewed what was known of the etiology of atherosclerosis and ischemic heart disease and recommended lines of research that might help to establish a clearer picture of the factors involved. Some of these recommendations have been followed; for example, the collection of data on deaths from ischemic heart disease in different countries, which is being done by WHO and the UN statistical service. A special unit has been created in WHO to deal with the cardiovascular diseases and consideration is being given to the best ways in which long-range epidemiologic, dietary, and clinical studies can be carried out.

The relationship between nutrition and the onset and course of other diseases such as diabetes and cancer is still obscure, but will no doubt become clarified as the work of other sections of WHO, such as the Cancer Unit, progresses.

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The Fragile Sex: Male or Female?*

Claire F. Ryder, M.D., M.P.H.

My duties with the Public Health Service in the United States, which concern the health of the aged, have frequently focused my attention on the increasing imbalance between male and female mortality rates in my country. I was especially reminded of this situation during the course of preparing replies to the questionnaire, "The Old Woman," distributed by the Medical Women's International Association as a preliminary to this Council meeting. I was led to a closer examination of both the mortality and disease experience of the two sexes in the United States and, as a corollary, the variations in social and economic background that surround these health situations. To present my material under a suitable designation, I have modified an expression used by Mr. J. O. Bond, who published an article some three years ago in the American journal *Geriatrics*, titled "The Fragile Male." Today I plan to discuss with you the relative "fragility" of the American man and the American woman.

An American professional woman speaking in Europe must ever keep in mind certain stereotypes of the "American female" that have gained currency in various parts of the world. It is often said of her abroad that she is the most fortunate woman in history, holding the economic reins, on the one hand, through her control of the national purchasing power and, on the other hand, exercising complete psychological and emotional dominance over the male members of her family. European authors who travel in the United States frequently encounter examples of this species, although I do not recall meeting any such women personally.

If, indeed, the American woman possesses an advantage over the American man, it is not to economics or sociology that we must look for the answer but rather to biology. Let us inquire more carefully into this matter in an attempt to determine whether the evidence indicates that the American woman is more robust than her male counterpart, not as a force in society but simply as a living organism. And, from a chivalrous respect for male sensibilities, let us consider first those health and other situations in which the American woman is clearly inferior to the man.

First, considering morbidity data, the endocrine diseases are the only major classification of illnesses in the United States to which women are more susceptible than men. Diabetes, for example, affects 50 per cent more women than men. Both goiter and gall bladder disease affect more women than men. Furthermore, there is a much higher mortality of cancer of the sex organs among women than among men.

As another measure of differentiation, deaths caused by accidental falls are more frequent among elderly women than elderly men; this may be related to the greater prevalence of vertigo among elderly women and to the fact that 9 elderly women out of 10 have trouble getting around in the dark (the same difficulty is encountered by only two thirds of elderly men).

Concerning the mental disorders of later life, Dr. Robert T. Monroe, in studying 8,000 patients more than 60 years of age, classified as "normal" only 40 per cent of the women, as contrasted with 59 per cent of the men.

In the field of economic status, it was reported in 1954 that, while less than half the

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men 65 years of age or more had incomes of under $1,000 a year, this situation prevailed with some five sixths of the women in that age group. Roughly 4 out of 10 aged women were reported as having no income at all in 1954, almost five times as large a proportion as was found among aged men.

Speaking as a woman, it is now my agreeable task to turn to those aspects of health and living in which we surpass the men of my country. First and foremost it is possible for us to reply to our male critics that "we survive."

In 1955 life expectancy at birth in the United States was 72.9 years for women and only 66.7 for men, an advantage of 6.2 years. Of course, American women are not unique in this survival superiority; it is shared by our sisters in other "developed" countries. The female "advantage" in life expectancy is 5.7 years for France, 5.5 years for England and Wales, and 4.5 years for Switzerland, Australia, and Japan. For an "underdeveloped" country such as India, by contrast, there is a male advantage in life expectancy of almost a year.

It has been observed that, under the harsh conditions of life in a rural primitive environment, male and female mortality tend to be similar; but it appears that progress toward industrialization and urbanization is accompanied by a growing female superiority in life expectancy. The experience of the United States, where the female advantage in this regard has risen steadily from 2 years in 1890 to 6.2 years in 1955, tends to corroborate this theory. Like all hypotheses, however, this explanation must still deal with stubborn exceptions. The highly advanced nation of the Netherlands, for instance, records a female survival superiority not much greater than that of Mexico (2.3 years, as compared with 1.9 years), although the Dutch woman may expect to live to be 73, while the Mexican woman may expect only 40 years of life.

Underlying the "advanced country" theory is the possibility, suggested by recent studies, that women have a better constitutional resistance to degenerative diseases and that, with the control over infectious diseases that modern civilization has achieved, woman's survival chances are actually enhanced by the emergence of the "chronic disease era" in which Europe and the United States are now living.

We do know that in the United States, at the age of 65 years, 30 per cent of the women and only 19 per cent of the men can look forward to reaching 85 years of age. At the age of 75 years, 4 out of 10 women and only slightly more than 3 out of 10 men can expect to live to 85.

Whatever the reason, a natural consequence of this female durability is a surplus of American women; in 1945, for the first time in our history, women exceeded men, and by 1958 there were 4 million more women than men in the United States.

This numerical advantage increases with age. Of the 16 million Americans aged 65 or older, about 55 per cent are women. It has been estimated that by the year 2000 there will be 145 aged women for every 100 aged men. No wonder that an American writer (male) recently commented testily that we are fated to become "a nation of old ladies."

When one considers the inevitable results of this survival superiority, one wonders just how much of an "advantage" it really is for American women. More than half the women in the United States of 65 years or more are widows; only one quarter of the men in that age group are widowers. Only 28 per cent of American women 75 years or more have avoided widowhood, while 62 per cent of American men of this age have escaped this fate. Since loneliness is the great curse of older age, is it an advantage that the average married woman in the United States can look forward to eight years of widowhood? And, in view of the fact that, even when pensions continue after the death of the husband, the widow's share is normally only from one-half to two-thirds full "retirement pay," financial insecurity may be expected to accompany loneliness in many cases.

Since heart disease is such a major factor in over-all mortality rates, a most important reason for the superior survival quality of the American woman is her strikingly greater resistance to that chief killer of our contemporary society. Metropolitan Life Insurance Company data for the years 1951-1953 reveal that, in the important age range of 40 to 74 years, the heart disease death rate in the United States was 872 per 100,000 for men and only 437 for women.

The American man is thus 100 per cent more vulnerable to this leading cause of death in this age group. Again, the international statistics from those countries where infectious diseases have been effectively brought under

control provide both illuminating parallels with the American experience and frank exceptions.

For England and Wales, Australia, Canada, and New Zealand the male heart disease death rate comes reasonably close to doubling the female rate, but in Switzerland, the Netherlands, and the Scandinavian countries the male death rate from this cause is only about half again as great as the female. It should be noted that, in this latter group of nations, the male rate itself tends to be less than half the American male heart disease death rate. In these countries also the gap between male and female life expectancy is less than in the United States. One must be cautious in drawing conclusions, however, even from this circumstance. Though tempted to theorize that, as the over-all heart disease death rate increases, the gap between the male and female rate widens, the Italian and French statistics must give us pause.

The French male death rate from heart disease was given as a low 337 for the 1951-1953 period, but this was still 72 per cent greater than the female rate. In Italy the rate for men was reported as only slightly higher than in France; nevertheless, this was only 13 per cent higher than the female rate of 321.

Even a superficial examination of the international mortality data for heart disease is enough to convince the observer of the dangers of hasty or oversimplified conclusions. At the same time, no area of research promises more rewarding benefits than this same field of international study. While much useful work of this type is now in progress (a good deal of it initiated by American scientists concerned with comparing the heart disease experience of specific racial groups in the United States with the experience in the "mother country"), still we have, I believe, only scratched the surface of what can be accomplished through this approach. The U.S. Public Health Service's National Institutes of Health in Bethesda, Md., have hopes and plans for a broadened program of research in this and related areas.

Of equal interest to American students of the subject is the fact that during the past 20 years there has been a 30 per cent increase in the cardiovascular-renal disease death rate for men and a 30 per cent decrease for women. Since the same phenomenon has been reported for ulcers, advocates of the "stress and strain" theory of heart disease causation in the United States have interpreted these data as supporting their hypothesis.

A recent study by two social scientists, however, points in another direction—the direction of an actual biological advantage enjoyed by women. Father Francis C. Madigan, a Jesuit priest, and Rupert B. Vance, a sociologist of the University of North Carolina, studied the comparative life expectancies of 30,000 Catholic Sisters and 10,000 Brothers in various teaching orders. All participants in the study were white, native-born, engaged in similar work, and equally free of financial and family worries. No drinking or smoking occurred in either group. If both men and women in this study are, therefore, to be regarded as being sheltered from conditions of "stress and strain," it is significant that the Sisters had a remaining life expectancy, at age 45, of 34 years, while the Brothers had a remaining life expectancy at the same age of only slightly more than 28 years. This is a difference in favor of the women of 5.5 years, or more than the difference reported for white men and women of age 45 in the general U.S. population (4.5 years).

Granted that the male is the more active and aggressive sex, and thus more susceptible to accidents and other hazards as well as to the stress and strain involved in economic survival, nevertheless, the Madigan-Vance study requires us to give serious attention to the "biological difference" hypothesis.

It is known that the average normal blood pressure of women is higher than that of men (156/84 mm. Hg for adult women and 145/82 for adult men), suggesting that women tolerate high blood pressure more safely than men.

Reasoning from the known sex differentiation of two X chromosomes in the woman as opposed to one X and one Y chromosome in the man, and from the more rapid development of the woman all the way from the prenatal stage to maturity, biologists have found it plausible to assume that this difference must extend to all types of physiological functioning, including resistance to disease.

When biology and statistics join hands in support of a certain approach to the explanation of phenomena, as in this instance, the burden of proof would appear to be on those who would deny an actual "built-in" superiority in resistance to disease in the woman. Or, in the more popular language of the title of this paper, the individual who would apply the term "fragile" to the woman rather than

to the man is faced with what we call in the United States "an uphill job."

Those who cling, however, to the nineteenth century image of the delicate, "fragile" woman may obtain some comfort from recent data concerning absenteeism in industry in the United States. Research workers have studied the record of 25 years of absence from the job caused by illness for 96 female employees (switchboard operators) and 116 male employees (linemen and installation workers) of the New York Telephone Company. During this long period the women lost on the average 313 days from work because of illness, while the men lost on the average only 124 days. Nor did menstrual disturbances explain this great difference, since they accounted for only one fourteenth of female illness reported. Respiratory infections, stomach upsets, muscle pains, and skin conditions were given as the major reasons for absenteeism in both sexes.

This apparent evidence of fragility in the American woman should not, perhaps, be too disconcerting for defenders of female durability. It is established that women take better care of their health than men. In the United States women average five and a half yearly visits to their physicians, as compared to four annual visits by men. Despite this, however, women spend less time in the hospital (excluding hospitalization for childbirth) than do men. Staying at home when one does not feel well is a sensible precaution. Dr. Lawrence E. Hinkle, Jr., who reported the results of the New York Telephone Company study, also commented on the "tendency of the American man to 'carry on, no matter what' as an added reason why male workers refuse to take to their beds when ill." In other words, it is suggested that men may be so determined to preserve the tradition of the "unfragile male" that they continue to work even when they should stay at home.

All in all, there is little evidence here to support Aristotle's somewhat jaundiced view of women, as illustrated by his opinion that ". . . the male is by nature superior, and the female inferior; and the one rules and the other is ruled: This principle, of necessity, extends to all mankind."

As we close our discussion of the relative fragility of the American man and the American woman, it should be noted that an effort has been made to achieve objectivity by introducing pertinent available data. As an American physician, I am anxious not to appear to be extrapolating the American patterns (especially those of life expectancy and of heart disease mortality) to the international scene. I confess, however, that the behavior of Mexican women, who insist on disrupting a pattern by outliving their men, and of Italian women, who prefer to match, rather than to cut in half, the heart disease mortality rate of their men, is quite provoking to the serious female international epidemiologist.

Fewer Patients in Mental Hospitals

According to Dr. Robert H. Felix, Director of the National Institute of Mental Health, Bethesda, Md., the trend toward wider use of psychic energizers, rehabilitation programs in the hospitals, outpatient clinics, and the admission of mentally ill patients to general hospitals has resulted in a lower number of inpatients in mental hospitals. From 1958 to 1959 there was a decrease of over 2,000 —the fourth consecutive year in which such a reduction was seen.

Bedroom Site of Most Fatal Home Accidents

Over 50 per cent of fatal home accidents occur in the bedroom, more than three times the accident rate in the next most dangerous areas, the living and dining rooms.

Medical Education of Women in Japan

Senzaburo Isoda, M.D.

THE TOKYO WOMEN'S MEDICAL COLLEGE, founded in 1900, was the first school built to educate women physicians and has continued to exist to the present time as a medical institution only for women. Not until 1945, the end of World War II, were women allowed to have equal opportunities with men in medical education as well as other fields of learning. At present, there are only about three to four women medical students in each class of the medical schools of universities or in each medical college.

At Tokyo Women's Medical College, where the present president is Naotaro Kuji, M.D., 300 women are studying medicine. In order to know the reason why the medical school for women needs to exist in this day of coeducation, the modern history of medical education in Japan and the purpose for founding the Women's Medical College need to be known.

About 100 years ago national institutions for medical education were established by the government for the first time in Tokyo and Nagasaki. These are the present schools of medicine of Tokyo University and Nagasaki University. Since then, other institutions for medical education were founded at various places. However, women were not allowed to attend. In 1877 a private institute for medical education, *Sai-sei Gaku-sha*, which literally means institution for saving lives, was opened, and women had their first opportunity to attend lectures with men. In those days a medical license was given to any man or woman who had an apprenticeship under a physician and who passed national board examination.

Dr. Isoda, Professor of Pediatrics, has taught at Tokyo Women's Medical College, Japan, for 28 years.

Although women physicians began to appear at that time, women were considered subordinate to men. Social activity by women was despised and thought to be disgraceful. It was regarded as presumptuous for women to study medicine. Women medical students were gradually rejected by men and finally *Sai-sei Gaku-sha* closed its doors to women on the grounds that they might disturb moral discipline. This meant that the first opening for women to the medical profession was again closed.

Dr. Yayoi Yoshioka,* a licensed physician, felt deep regret about this matter. She believed that in order to elevate the low social status of women it was necessary for them to have economic independence. Considering the nature of the medical profession and a medical career suitable and honorable for women, she founded a woman's medical college in 1900, the beginning of the Tokyo Women's Medical College.

Since its foundation, the College has encountered rejection and oppression; however, by struggling against hatred, obstacles, and administrative difficulty, many women physicians have gained a footing in society. Because it was established for such an aim, the College's history, tradition, and principles are that it should be exclusively for women. For this reason it exists as a woman's medical college even today.

After the opening of Tokyo Women's Medical College two other privately owned women's medical colleges were built—in 1924 and 1928 respectively. At that time about 450 women medical students in all were graduated annually from these three medical colleges.

*Dr. Yoshioka, the first president and founder of Tokyo Women's Medical School, now Tokyo Women's Medical College, and Japan's pioneer woman physician, died on May 23, 1959, at the age of 88. She had taught at the Medical School and College for more than 50 years and helped to establish hospitals in Tokyo.

When World War II began there was a shortage of physicians, and six other women's medical colleges were set up; however, they were all privately owned and the government had nothing to do with them.

In 1945, after the end of the War, the educational system in Japan was changed to allow for coeducation. Women were then allowed to attend any medical school. Therefore, the women's medical colleges except for Tokyo Women's Medical College were closed or became coeducational institutions. Although the door of medical school was opened to women, only three or four could be admitted to each one.

At present, the total number of women medical students, including the 300 at Tokyo Women's Medical College, is about 900 to 1,000. According to the present system of education in Japan, after six years of primary school, three years of middle school, three years of high school, six years of medical school, and one year of internship, the students are qualified to be physicians. Every year the ratio of those who pass the national board examination is about 3,000 men to 250 women.

Some women engage in research work after graduation, and the rest go into practice after several years of training in a hospital. There are many who practice medicine while raising a family. They are relied upon by lay persons and are busy in clinics or in health guidance work. This fact should prove the suitability of women as family physicians. On the other hand, a certain number of women major in basic science or stay in teaching positions.

The number of women physicians in Japan is about 10,000, of which 4,000 are graduates of Tokyo Women's Medical College. Up to now, about 450 of them have received a Ph.D. or Sc.D. in medicine.

The Emperor makes it a rule to attend the opening session of the quadrennial Japanese medical congress and in the spring of 1959 Their Majesties, the Emperor and the Empress, paid a visit to the fifteenth congress of the Japanese Medical Association. It was the first time for the Empress to appear at the congress, and it is believed that her attendance was especially for the women members of the association.

As explained, the activity of women physicians in the society and in research has been recognized and appreciated in Japan. There is no distinction made now between the sexes as physicians; however, as women have their own characteristics, it is hoped that they demonstrate features of womanhood in medical practice.

Office Management of Psychosomatic Disorders

At the Tenth Annual Lecture Series on Psychiatry given at the North Shore Hospital, Winnetka, Ill., Dr. Jules H. Masserman, Professor of Neurology and Psychiatry at Northwestern University College of Medicine, urged physicians to exercise prudence in treating patients with emotional ills. "Accept each patient, not as an interesting case in support of some preconceived theory or as an object of objective diagnosis or even as grist for another therapeutic mill, but as a hurt, frightened, and troubled human being seeking relief and guidance."

The Chicago psychiatrist gave these additional suggestions: 1. Beware of iatrogenic illness, as a dolorous shake of the physician's head can often cause more harm than actual physical pain. 2. Do not detract from the authoritative or parental image of the family physician. 3. Skillfully utilize every medical means available to relieve bodily pain and dysfunction and suspend undesirable activities. 4. Assist the patient in adopting new patterns of conduct and reorietation. 5. Use reason, demonstration, and personal example to re-educate the patient. 6. Utilize every available form of social participation to gain enlightened self-interest.

CASE REPORT

A Hypogastric Mass That Presented a Diagnostic Problem*

Diosdada Torrijos, M.D., and Fe del Mundo, M.D.

A CASE OF HYPOGASTRIC MASS in a 13 year old girl is reported because of the time spent in diagnostic examinations and differential diagnosis before it was realized that awareness of the condition could have avoided most of the tests and limited the diseases under consideration. A few lessons may be derived from errors of omission in the diagnosis of this patient.

REPORT OF A CASE

A 13 year old Filipino girl was admitted to Far Eastern University Hospital on Jan. 31, 1958, because of an abdominal mass of one week's duration.

The patient had been well until two weeks prior to admission, when she felt vague pelvic pains associated with some discomfort on voiding. Pain was most intense after every micturition. The urine, however, appeared normal, and there were no other constitutional symptoms. About one week before admission, the patient accidentally palpated a mass below the umbilical region; it measured about 2 by 2 cm. in diameter, had ill-defined borders, and was nontender, nonpainful, and slightly movable. This mass gradually enlarged, and, because of persistent pelvic pains and discomfort on voiding, medical consultation was sought; subsequently, hospitalization was advised.

Physical examination revealed a fairly well-developed, fairly well-nourished, conscious, ambulatory, co-operative patient. The abdomen was not distended, and there were no visible or superficial veins. Liver and spleen were not palpable. An elongated, doughy mass, 4 by 4 in. in diameter, was felt from the umbilical region toward the suprapubic area. The upper pole was rounded and free. The mass was slightly movable and nontender, with well-defined borders; there was no rigidity or muscle guarding. The rest of the physical examination was negative. The impressions on admission were: intra-abdominal new growth (neuroblastoma), polycystic kidney, and ovarian cyst.

A complete blood count, routine urinalysis, stool examination, and chest roentgenography were essentially negative. Roentgenography of the abdomen with the patient in lying and upright positions revealed both kidneys to be normal. However, a soft tissue density distinct from the kidney outlines was visualized in the umbilical region. A barium enema revealed an intraluminal and extraperitoneal mass at the hypogastrium, pushing the sigmoid upward. It was noted that, when the patient was given a cleansing enema in preparation for the barium enema, she had a bloody return flow. A rectal examination did not show the presence or nature of the mass. After the examinations, the case was referred to surgery and the patient was scheduled for a laparotomy.

In the ward, the patient remained afebrile, active, and co-operative; occasionally, especially at night, she complained of pelvic cramps. There were no other complaints.

A preoperative obstetric-gynecologic clearance was scheduled. On inspection of the patient's genitalia by a consultant, the labia were found to be blu-

* Reprinted with permission from *The Philippine Medical World 19:* 437-439, Nov., 1958.

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ish red and the vaginal orifice showed a bulging membrane. The hymen was imperforate. A diagnosis of hematocolpos plus probable hematometra was made.

A simple incision of the imperforate hymen was done and about a liter of chocolate-colored fluid was obtained and drained. Immediately the patient felt much relieved, and the elongated mass disappeared. The patient was given a penicillin-streptomycin combination and ergonovine maleate (Ergotrate), 1/320 grains three times a day for three days. She was discharged and advised to come regularly for vaginal dilatation and also for further examination, to look for any possible congenital anomaly that could occur with the imperforate hymen.

DISCUSSION

When this girl was referred to the Department of Pediatrics for examination, the presence of a hard mass in the lower abdomen readily made the pediatric staff and interns consider all masses that could possibly arise in that location.

As in most teaching institutions, one diagnostic procedure led to another, and all possible conditions were included in the differential diagnosis. A hard, smooth, rapidly growing mass in the hypogastrium that was causing pressure on the bladder and even in the rectum could certainly be a cause for worry and prompted a surgical consultation. An unnecessary laparotomy would have been performed but for a gynecological clearance preparatory to surgical intervention.

Aware of gynecologic problems in a child of this age, it did not take the gynecologist five minutes to discover a condition that neither the pediatrician nor the surgeon nor the radiologist ever thought of. In retrospect, it was a simple case of blood accumulation in the uterus and vagina of a girl who should have started to menstruate. This was the age to expect menarche; the location and shape of the mass should have called attention to the possibility of the uterus; the absence of constitutional symptoms and her referred pains and discomfort were points that should have served as guides. All these were overlooked for want of awareness of gynecologic problems among the pediatricians.

SUMMARY

A case is reported of a 13 year old girl with a hypogastric mass, noticed one week before admission, that caused discomfort and other pressure symptoms. There were no accompanying constitutional symptoms. Notwithstanding the laboratory examinations and a fairly extensive differential diagnosis that was considered, the diagnosis was not conclusive.

Lack of awareness of gynecologic problems in childhood, greater consciousness of tumors, the excitement over a rapidly growing mass, and the eagerness to intervene with surgery were points that accounted for failure to consider a gynecologic condition.

Upon gynecologic clearance preparatory to surgical intervention the child was found to have an imperforate hymen, hematocolpos, and hematometra, which were relieved immediately by incision of the hymen and drainage of accumulated blood.

Pamphlets on Mongolism and Cerebral Palsy

Two pamphlets, prepared by the National Institute of Neurological Diseases and Blindness, were published this year, one on mongolism and the other on cerebral palsy. Written for the layman, the text includes signs, causes, and prevention of the disease; the research in the field; agencies to be consulted for help and information; and a bibliography of helpful books and articles. The pamphlets, "Mongolism: Hope Through Research" (Public Health Service Publication no. 720; Health Information Series no. 94) and "Cerebral Palsy: Hope Through Research" (Public Health Service Publication no. 713; Health Information Series no. 95), are available from the Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C., for the price of 5 cents each.

Medical Briefs

POLYVALENT INFLUENZA VACCINE

Speaking at the International Conference on Asian Influenza earlier this year, Dr. Fred M. Davenport, Professor of Epidemiology at the University of Michigan and Director of the Commission on Influenza of the Armed Forces Epidemiological Board, presented the results of tests with a polyvalent influenza vaccine in a mineral oil emulsion. Over 100,000 doses were administered in field trials and were well tolerated; the vaccine has proved effective for three years.

Investigators believe that there are six major "families" of influenza virus and that this vaccine would afford protection against all six. In the event of the development of a new strain of flu virus, Dr. Davenport maintained that "use of the old formula would probably yield better protection than no vaccine at all." Laboratory tests have shown the vaccine to be effective even when the offending organism is not opposed by its specific antigen.

The mineral oil emulsion has the advantages of allowing for the inclusion of several strains; conserving the antigen, thus prolonging the protection; and of being free of agents that might produce local necrosis, as seen in alum-precipitated antigens.

This report was discussed by Dr. Jonas E. Salk of the University of Pittsburgh, who supported Dr. Davenport's conclusions.

EFFECTS OF NEWER DIURETICS

Newer diuretics are proving effective at one one-hundredth the dose of earlier thiadiazines, and show signs of overcoming one of their unwanted effects, the excretion of potassium. This was announced by two Philadelphia physicians who addressed a conference on edema and hypertension in May.

Dr. Morton Fuchs of Hahnemann Hospital, Philadelphia, reviewed use of the older and newer thiadiazine drugs plus a new phthalimidine compound from Switzerland. Dr. Fuchs said that he and Dr. John Moyer, coauthor of the reports, have now studied exhaustively more than 500 patients. Chlorothiazide and flumethiazide were administered in daily doses of up to 2 Gm. for best results, but when hydrogen atoms were added to these two drugs the maximum daily dose was reduced to about 300 mg.

The scientist reported that two more recent and more complex derivatives of these drugs, 3-benzylhydroflumethiazide (Naturetin) and trichlormethiazide (Naqua), were effective in doses of 1 to 10 mg. Three still newer derivatives are being tested by the Hahnemann investigators, making eight new drugs in this field since the discovery of chlorothiazide.

The two newest drugs seem to cause less voiding of potassium by the body over a 48 hour test period. Dr. Fuchs does not know whether there will be any difference in potassium excretion over a longer dosage period, such as is necessary in patients with chronic heart failure.

ENDOMETRIAL HORMONES AND ABORTION

A hormone imbalance in the endometrium as a factor in abortion was considered by Joseph T. Velardo, Ph.D., an endocrinologist from Yale University School of Medicine, at the 15th Annual Meeting of the Obstetrical and Gynecological Assembly of Southern California. In experiments conducted on pregnant albino rats, a definite correlation was found between the ratio of estraniol, estrone, estriol, and 16-epiestriol, and successful pregnancies. It became evident that any change in the ratio of hormones could be directly associated with the resultant abortion. Dr. Velardo believes that the clinical application of this research will benefit the victims of habitual abortion.

EARLY FITTING OF HEARING AIDS

Children under 3 years of age can be successfully fitted with hearing aids, according to Dr. Adam J. Sortini of the Children's Hospital Medical Center in Boston. The children attain greater facility in speech and language learning and improve in their behavior. Sixty children were included in the test, all of whom had above normal intelligence and suffered hearing losses from 57 to 92 db.

The changes in these children were observable very soon after they were fitted with hearing aids. They began to babble while at play, to imitate speech, and to respond to the people around them. Behaviorially, these children had fewer temper tantrums and crying spells. At the end of three years, 52 of the 60 children were able to wear their hearing aids throughout the day.

World Health Organization

NINE COUNTRIES JOIN WHO

Nine new members or associate members, eight of them in Africa, were unanimously admitted to the WHO in May. The election took place at the thirteenth World Health Assembly in Geneva. The new admissions bring the membership of the organization to a total of 89 full and 10 associate members.

Cameroun and the Republic of Togo were admitted as full members; the new associate members are Cyprus and six members of the French Community—the Central African Republic, the Republic of the Congo, the Republic of the Ivory Coast, the Gabon Republic, the Republic of the Upper Volta, and the Republic of the Niger.

Welcoming the new members, A. Asumda of Ghana said, "Today a great wave of nationalism sweeps over Africa with the emergence of new nations. WHO should look forward to many more applications for membership from the African region."

SMALLPOX IN 1959

Some 72,000 cases of smallpox were reported in 1959 throughout the world (outside mainland China), according to the WHO Weekly Epidemiological Record. In 1958 a total of 242,000 cases—an unusually high number—was reported. The improvement was attributed to the fall of the incidence in India and East Pakistan where, after the unusually high levels of 1958 (with about 218,000 cases), only 50,000 were reported during the year. Smallpox incidence has not decreased to any considerable extent outside India and East Pakistan. About 22,000 cases were recorded during the year, against 24,000 in 1958, in Asia (outside India and Pakistan), in Africa, and in South America.

In ports and towns served by an international airport, the highest number of smallpox cases was recorded in India (Madras 2,129, Cochin 633, Bombay 519, and Delhi 401 cases) and other countries of Asia (371 in Makassar, Indonesia, and 341 in Rangoon, Burma), but sporadic cases were also reported in a number of ports and airports of Africa and South America. All cases on board ship or brought by air during the year originated in Asia.

About 14,000 cases were recorded in Africa, excluding Liberia; 1958 statistical returns show a total of about 15,000 cases in Africa outside Liberia, where 5,000 cases were reported. In 1959 the number of cases decreased in the seven territories of former French West Africa from 7,000 to about 4,000 but rose in the Belgian Congo from 1,300 to 2,500.

Some 3,000 cases were recorded in the Americas. The main centers of smallpox were reported in Brazil, Colombia, and Ecuador.

In Asia the total number of cases fell in India from 168,000 to about 43,000. The highest incidence was recorded in Orissa (about 8,000 cases, or 55 per 100,000 population).

In Europe imported infection accounted for 19 cases at Heidelberg (German Federal Republic) in January, 1959. One case, imported by air from India, was reported in East Berlin. A single case was reported at Liverpool, United Kingdom. In the U.S.S.R. a single case was reported at Termez in the Uzbekistan S.S.R.

MONEY FOR MALARIA

In the WHO Director-General's report for 1959 it was stated that 95.3 per cent of the contributions to the Malaria Eradication Special Account were from the United States. Dr. Leroy Burney, Surgeon General of the U.S. Public Health Service, expressed hope that the action of certain members would stimulate wider recognition of the urgent need for larger contributions of a more international character. If the world malaria eradication campaign should fail, Dr. J. Stralau of the Federal Republic of Germany foresaw "very serious repercussions," and he announced that his government had agreed to contribute 750,000 marks (about $180,000) both in 1960 and 1961, over and above the $95,000 already contributed to the Malaria Eradication Special Account. "It will be difficult for us to obtain further credits if we cannot report new contributions from other countries to our parliamentary authorities."

A contribution of £1,000 was promised by Ghana.

Dr. A. Arreaza Guzman of Venezuela reported that Venezuela had achieved malaria eradication with its own resources, although he paid tribute to the help of internationally trained experts.

President's Message

The preparation of a paper for the Medical Woman's International Association meeting in Baden-Baden on the general theme "The Old Woman" proved to be a difficult task even to start. The term itself, at least in the United States, was not one that evoked anything but a feeling of discomfort, particularly among those of us who envision a stereotype when it is used. The task was made even more difficult because of the many facts and figures uncovered by library research.

One fact did stand out, however, in all these data—the "old woman," although similar in many respects to her male counterpart, was also quite dissimilar to him from both a mortality and morbidity viewpoint. This dissimiliarity thus became the topic of my paper. To find an appropriate title was the next step. As a public health physician I was most familiar with the type found in our specialty journals and so I tried "An Epidemiologic Consideration of the Mortality and Morbidity Differential of Men and Women in the United States Today." But this seemed much too learned for the proposed paper and in fact threatened to overwhelm it. Next I considered a simpler title—"Vive la Difference!" But this was too flip. Thus I arrived at the compromise of the title of the paper printed in this issue of THE JOURNAL—"The Fragile Sex: Male or Female?".

Note that this is a question, and factual evidence is presented to help the reader answer it. I know that we can all add empirical evidence to support the fact that the day of the frail woman, subject to the "vapors" and prone to delicate and frequent sniffs of her smelling salts, is gone forever. One has only to glance through recent newspaper reports to gather the evidence.

One newspaper article told recently of a woman weighing scarcely 100 lb. who alone had lifted the end of her station wagon when her son was pinned under it. In another instance a scientist, being interviewed about the possibility of sending someone into space in the near future, admitted (I hope not with too much reluctance) that the best person to send because of psychological and physiological stability would be a carefully selected pregnant woman.

So, with women gaining on the men in all spheres, whether in work or play, in sports or profession, and now perhaps even in outer space, we all would do well to re-examine the question of which is the fragile sex.

Claire F. Ryder M.D. M.P.H.

THE UNITED NATIONS

1945—Hope of the World—1960

Ada Chree Reid, M.D.

On June 26, 1945, delegates from 50 nations—representing the great majority of mankind, some 1.7 billion persons—resolved to combine efforts to make a secure and better world through "an international organization to be known as the United Nations." On that day in San Francisco they signed the UN Charter. The UN came into existence officially on Oct. 24, 1945, when the Charter had been ratified by a majority of signatories. And, by resolution of the General Assembly, Oct. 24 has been set aside to be observed as UN Day in every member nation.

To maintain international peace and security; to develop friendly relations among nations based on the equal rights and self-determination of peoples and to take other appropriate measures to strengthen peace; to achieve co-operation in solving international economic, social, cultural, and humanitarian problems and in promoting and encouraging respect for human rights and fundamental freedoms for all without distinction of race, sex, language, or religion; and to be a center for harmonizing the actions of nations in achieving these ends—these are the purposes of the UN.

The UN is the one meeting place where the representatives of 82 nations, spokesmen for all political views, social systems, cultures, and religions, are freely heard.

It is indeed the "hope of the world," as Judge Dorothy Kenyon wrote in the UN number of THE JOURNAL, (*3*:418-419, Oct., 1948), a world still split by racial, religious, and ideologic differences. Agreement has not been reached on many problems, such as disarmament, nuclear testing, and the ever-present Berlin crisis. But much has been achieved during these 15 years. First and foremost, peace has been maintained through these turbulent years, while empires have vanished and many new nations have emerged ready for independence.

Far-reaching economic changes have taken place; great progress has been made in health, education, and improved living conditions throughout the world. Much remains to be done, it is true. The record of the UN is far from perfect, but as Secretary-General Dag Hammarskjold has pointed out—

> We should recognize the United Nations for what it is—an admittedly imperfect but indispensable instrument of nations working for a peaceful evolution toward a more just and secure world order. At this stage of human history, world organization has become necessary. The forces at work have also set the limits within which the power of world organization can develop at each step and beyond which progress, when the balance of forces so permits, will be possible only by processes of organic growth in the system of custom and law prevailing in the society of nations.

For the United Nations, it must be remembered, has none of the powers of a world government.

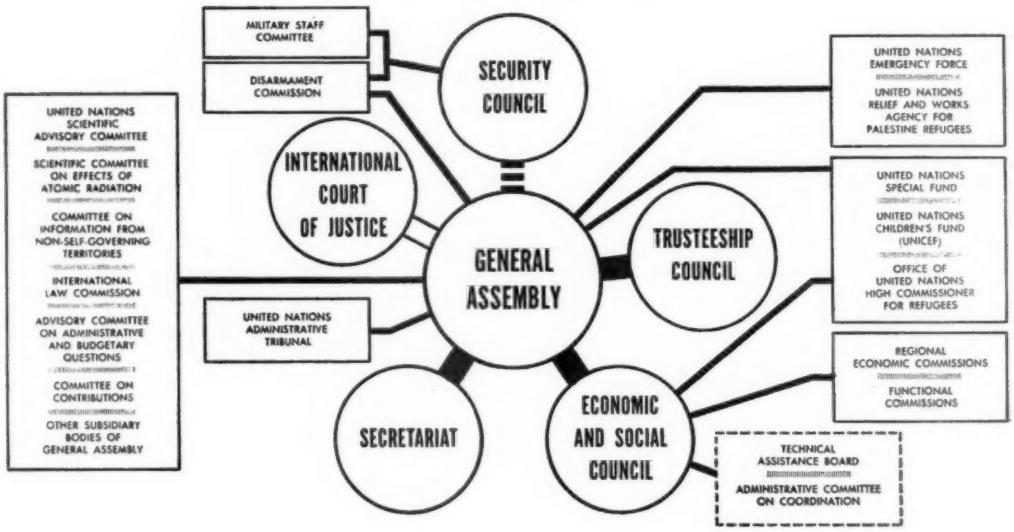
> It is a framework for diplomatic operations and the power of decision remains, in almost all cases, with the Member governments. Beset as we are with what often seem to us to be the truly desperate anxieties of our age, it is easy to be impatient with both the evident weaknesses of world organization as thus

constituted and the new complexities of international relations which it reflects.

The better we understand the policies, procedures, and problems of the UN, the more we can appreciate what really great progress has been made in these 15 critical years. To aid in this understanding, subsequent articles will appear in THE JOURNAL relating to the various agencies and commissions in the framework of the UN.

For we believe that knowledge will bring understanding, and understanding will bring support.

THE UNITED NATIONS


MILITARY STAFF COMMITTEE
DISARMAMENT COMMISSION
SECURITY COUNCIL
UNITED NATIONS EMERGENCY FORCE
UNITED NATIONS RELIEF AND WORKS AGENCY FOR PALESTINE REFUGEES
UNITED NATIONS SCIENTIFIC ADVISORY COMMITTEE
SCIENTIFIC COMMITTEE ON EFFECTS OF ATOMIC RADIATION
COMMITTEE ON INFORMATION FROM NON-SELF-GOVERNING TERRITORIES
INTERNATIONAL LAW COMMISSION
ADVISORY COMMITTEE ON ADMINISTRATIVE AND BUDGETARY QUESTIONS
COMMITTEE ON CONTRIBUTIONS
OTHER SUBSIDIARY BODIES OF GENERAL ASSEMBLY
INTERNATIONAL COURT OF JUSTICE
GENERAL ASSEMBLY
TRUSTEESHIP COUNCIL
UNITED NATIONS SPECIAL FUND
UNITED NATIONS CHILDREN'S FUND (UNICEF)
OFFICE OF UNITED NATIONS HIGH COMMISSIONER FOR REFUGEES
UNITED NATIONS ADMINISTRATIVE TRIBUNAL
REGIONAL ECONOMIC COMMISSIONS
FUNCTIONAL COMMISSIONS
SECRETARIAT
ECONOMIC AND SOCIAL COUNCIL
TECHNICAL ASSISTANCE BOARD
ADMINISTRATIVE COMMITTEE ON COORDINATION

ATTENTION! AMWA MEMBERS

Can You Help Us Locate the Following Women Physicians?

Mary A. Churchill	May Maher	Gizzella Wittman	Marjorie Hayes
Grace Edwards	Selma M. Olson	Virginia Smith-Howard	Dorothy Henderson Heilman
Mariana Hoyt Henry	Pauline E. Rapp	Frances E. Noblin	Elizabeth McNaughton
Jessie MacDonald	Helen Semenko	Eugenia Hayes	Emily Simms Haller

It will be appreciated if anyone knowing the current addresses of these physicians will send the information to the American Medical Women's Association, Inc., 1790 Broadway, New York City 19.

Of Special Interest

JEFFERSON ADMITS WOMEN

Jefferson Medical College of Philadelphia, the largest private medical school in the Nation, with a freshman class of 175, has opened its doors to women students this fall. Woman's Medical College of Pennsylvania, established in 1850, is now the only medical school that is not coeducational.

PROJECT HOPE ENDORSED BY AAGP

The Nation's family physicians formally endorsed Project HOPE, a plan that will send four modern hospital ships to ports of call around the world, at the meeting of the American Academy of General Practice in Miami Beach, Fla. The Board of Directors affirmed its enthusiasm with a $1,000 contribution. The Academy further urged its 26,000 members to volunteer for either one year or two month tours of duty on one of the four newly equipped ships.

Dr. Floyd C. Bratt of Rochester, N.Y., the Academy's President-Elect and Chairman of the Project HOPE Committee, said, "The Academy believes that trained family doctors can make continuing contributions to medical care standards in all parts of the free world. They not only can treat patients but they can pass along, to doctors and technicians in other lands, up-to-date diagnostic and therapeutic techniques."

MEAT AND CHOLESTEROL

Trappist monks, who eat no meat, have lower serum cholesterol levels than Benedictine monks, who do eat meat. These findings were reported by a group of scientists who are conducting a study of cholesterol with the support of the National Heart Institute.

The stability of monastic life and the similarities between the two communities, the researchers suggest, make the two groups suitable subjects for comparison in such a long-term study. They also point out that the Trappists are withdrawn from the world, devoted to contemplation, prayer, and physical labor; they neither drink nor smoke. The Benedictines are teachers and preachers, involved with the world and its ways, and neither drinking nor smoking is prohibited for them.

Results in the first year, in which blood was analyzed four times, bear out the contention of cardiologists who maintain that diets high in animal fat cause serum cholesterol levels to rise. Trappist monks in their twenties had serum cholesterol levels averaging 184 mg. per 100 cc.; a peak of 220 mg. was reached when the monks were in their fifties; and a drop to 212 mg. was recorded when the monks were in their sixties. For Benedictine monks in their twenties the average level was 223 mg., reaching a peak of 258 mg. in the monks' fifth decade. The serum also was analyzed for other fatlike substances and, in each case, the values were comparably higher for the Benedictines.

The study originally involved only 70 Benedictines and 80 Trappists. The success of the first year program has led to the inclusion of 500 subjects in order to provide valid epidemiological data.

EDUCATION OF GIRLS IN AFRICA

What opportunities exist in African countries for the education of girls, and what are the economic and social factors that encourage or prevent them from taking advantage of these opportunities? These are the problems that were discussed in Cotonou, Dahomey, at a meeting of African women educators. The meeting, held from May 24 to June 2, was organized jointly by the Government of Dahomey and UNESCO.

Discussions were devoted mainly to problems concerning the availability of primary education and secondary general, technical, and vocational education to girls in Tropical Africa. Measures being taken or planned in the various countries were also reviewed, and the educational leaders suggested priorities for national, regional, or international programs to be undertaken in Tropical Africa during the next few years. Among those participating were advisers to ministries of education, school inspectors, and teachers, representing 14 countries and territories.

The report of the meeting will be distributed to educational bodies and to women's organizations, and will be discussed at the United Nations seminar on the participation of women in public life, to be held in Addis Ababa from Dec. 12 to Dec. 23, 1960. (UNESCO)

Opportunities for Women in Medicine

AWARDS

Cancer Research. The General Assembly of the United Nations has instituted prizes totaling $100,000, to be awarded for the most outstanding scientific research work on the causes and control of cancerous diseases. Complete information can be obtained from the Editor, UNESCO Features, UNESCO Headquarters, Paris, France.

FELLOWSHIPS AND GRANTS

Nutrition. Wesson, world's largest cottonseed oil company, has announced that it is accepting applications for financial grants from nonprofit research centers at universities, hospitals, and laboratories, as well as from private individuals whose primary work is in nutritional research. The newly established annual grant of $100,000 is for basic and clinical research in the field of edible fats and oils. In addition to the money awarded, Wesson will provide, without cost, pure cottonseed oil of a constant composition for specific research projects. All decisions regarding the awards will rest with a board of medical advisers representing the major fields of cardiology, general nutrition, gastroenterology, biochemistry, and pediatrics. For more information contact the Wesson Fund, 1 E. 45th St., New York City 17.

Orthopedics, Preventive Medicine, and Rehabilitation. The National Foundation, in addition to its fellowships offered in the field of arthritis (see THE JOURNAL, Jan., 1960, p. 71), is offering fellowships to provide research training in the fields of medicine and the related biological and physical sciences through the participation of the fellow in a specific research project. The candidate must have an M.D. degree, be a U.S. citizen, and be in sound health. The fellowship will be for one or two years, although extensions are occasionally granted. The three basic stipend levels are $4,500, $5,460, and $6,420 per year with $540 a year for each dependent and an annual increase, usually of $480. The maximum stipend is $8,000 per year. A transportation allowance not to exceed $600 will be allowed for fellows approved for study overseas. The fellowship requires full-time participation in the research program of the fellow's choice.

The Foundation is offering a fellowship to prepare orthopedists for filling academic positions in schools of medicine. The candidate must have, in addition to the afore-mentioned requirements, a license to practice medicine in one or more states and must have completed the requirements for certification by the American Board of Orthopaedic Surgery or equivalent training. The age limit is 36 years. The program of study includes full-time advanced clinical study and research in a center associated with a medical school that offers specialty training in orthopedic surgery approved by the AMA's Council on Medical Education and Hospitals or in an institution abroad that offers a well-developed program in orthopedics.

In the field of preventive medicine, The Foundation is offering fellowships for study and research in the teaching of preventive medicine, in order to prepare physicians for filling teaching positions in medical schools and schools of public health. To be eligible, the physician must have completed a one year internship in an approved hospital and have not less than two years of training and experience in one of the areas related to preventive medicine, which shall have included responsibility for teaching, plus the general requirements.

For physicians interested in rehabilitation, fellowships are offered to maintain and improve the quality of comprehensive care by providing clinical experience in rehabilitation for all qualified physicians and by providing the opportunity for advanced study to physicians who have completed specialty training in physical medicine and rehabilitation. These physicians should propose programs for advanced study in the field. For physicians who have not completed specialty training in this field, programs should be selected that will place special emphasis on rehabilitation in relation to their individual medical specialties. For these fellows, fellowships will be awarded for six months to one year and are subject to renewal. Closing dates for all applications are Feb. 1, Aug. 1, and Nov. 1 of each year. For applications and further information write

to The National Foundation, 800 Second Ave., New York City 17.

MEETINGS

Clinical Science. The Association of Clinical Scientists will hold its Annual Meeting on Nov. 6 at the Shoreham Hotel, Washington, D.C. Information on the meeting can be obtained from Dr. Robert P. MacFate, 54 W. Hubbard St., Chicago 10. The Association will hold its Applied Seminar on Measurements of Pancreatic Function in Clinical Medicine Nov. 4-5. Information on the Seminar can be obtained from Dr. F. William Sunderman, 1025 Walnut St., Philadelphia 7.

Psychiatry. The Third World Congress of Psychiatry, to meet June 4-10, 1961, Montreal, Canada, is being held at the invitation of McGill University and under the auspices of the Canadian Psychiatric Association. Meeting on the American continent for the first time, the Congress is expected to attract some 3,000 delegates from 62 nations. The fields of psychiatry, general medical practice, psychology, biochemistry, nursing, sociology, anthropology, social work, and pharmacology will be represented. Copies of the second announcement, which carries information regarding the program and registration, may be obtained by writing the General Secretary, III World Congress of Psychiatry, 1025 Pine Ave. W., Montreal 2, P.Q., Canada.

Psychoanalysis. The Scientific Sessions of the Mid-Winter Meeting of the Academy of Psychoanalysis will be held Dec. 10-11 at the Hotel Biltmore in New York City. The theme of the first day's meeting will be "The Role of Values in the Psychoanalytic Process." The following four papers will be presented on the first day: "Values, Truth and Psychoanalysis," John R. Reid, Ph.D.; "Values, Maturation and Health," A. N. Maslow, Ph.D.; "Value Differences Between Patient and Psychoanalyst," Janet MacKenzie Rioch, M.O.; and "Values, Identity and Psychoanalysis," Marianne N. Eckhart, M.D. The second day's meeting will be devoted to a series of papers by members of the Academy. Inquiries may be addressed to Joseph N. Merin, M.D., Secretary, the Academy of Psychoanalysis, 125 E. 65th St., New York City 21.

Tropical Medicine. The American Society of Tropical Medicine and Hygiene will hold its meeting Nov. 2-5 at the Biltmore Hotel in Los Angeles. For information write to Dr. Rolla B. Hill, 3575 St. Gaudens Rd., Miami 33, Fla.

BRANCH NEWS

BRANCH THREE, MARYLAND, invited BRANCH ONE, WASHINGTON, D.C., to its regular meeting on Dec. 3, 1959, to fete Dr. P. S. Bordeau-Sisco on the occasion of her ninetieth birthday. Her natal day was actually Nov. 26, but the branches chose the occasion of their regular meeting to effect a complete surprise.

Dr. Bordeau-Sisco was presented with a corsage of violets, "sweet speeches," beautiful flowers, a birthday cake, and a silver pin. The history of her life was read by Dr. Roselva Thompson-Daugharthy.

Dr. Bordeau-Sisco was instrumental in organizing both Branch One and Branch Three, and still attends all meetings of Branch Three from October to May.

INTERNATIONAL NEWS

Dr. F. Mary Ershine Longwood of Belfast, Ireland, has informed us that during the year 1959-1960 five meetings of the Medical Women's Federation of the Northern Ireland Local Association were held in addition to the annual general meeting. In April, 1959, Dr. Muriel Frazer gave a paper on "Neonatal Emergencies." In June the Association discussed the memorandum to be submitted to the Departmental Committee, inquiring into the practice of artificial insemination. In October meetings resumed with Dr. Kathleen Cathcart's presidential address on "The Maternity World To-day and Yesterday." In December Mrs. Beatrice Lynn repeated her presidential address to the Irish Ophthalmological Society, given first at its joint meeting with the Royal Society of Medicine in Belfast in May, 1959. In May, 1960, the Council of the Medical Women's Federation met in Belfast. Business meetings occupied one and a half days and were attended by many of the local members. The Council members appeared to enjoy their stay in Belfast, especially the dinner at Stormont and the Saturday afternoon drive to Cushendun.

News of Women in Medicine

Drs. Genevieve M. Bader, Rose Ruth Ellison, and Lois Murphy, all members of the Memorial Sloan-Kettering Cancer Center faculty, New York City, were among the officers of instruction for the American College of Physicians' postgraduate course, "Cancer and the Internist—1960 Concepts." The course was held Oct. 10-14.

Participating in the transcontinental Powder Puff Derby, a competition for amateur women pilots, were Drs. Margaret Densmore and Constance Volk of Media, Pa. The physicians flew a 2,509 mile run beginning at Terrence, Calif., and ending at the New Castle County Airport near Wilmington, Del.

On July 1 Dr. Martha May Eliot, Head of the Department of Maternal and Child Health, Harvard Medical School, retired and became emeritus professor of maternal and child health. Retiring at the same time was Prof. Bertha Shapley Burke. The two became the third and fourth women to be so honored at Harvard.

Dr. M. Jeanne Fairweather, Brooke Army Medical Center, Fort Sam Houston, Texas, was honored in July by an awards dinner at the Fort Sam Houston Officer's Club prior to presentation of a citation award as outstanding woman in the field of medical services among the alumnae of the Incarnate Word College in San Antonio.

Dr. Emma Jane Freeman of Buckhannon succeeded to the directorship of the Division of Maternal and Child Health of the West Virginia State Department of Health in July.

Dr. Grace A. Goldsmith, Professor of Medicine at Tulane University School of Medicine, New Orleans, was chairman of the panel on Evaluation of Nutritional Status in Man, presented Sept. 1 at the Fifth International Congress on Nutrition held in Washington, D.C.

Dr. Edith Klemperer of New York City spoke on the subject "Hypnosis in the Control of Pain" at the Conference on the Uses of Hypnosis in Medicine, Dentistry, and Psychology of the New Jersey Section of the Society for Clinical and Experimental Hypnosis and the Department of Psychology at Rutgers University.

Addressing the Pennsylvania chapter of the American College of Chest Physicians and the Pennsylvania Trudeau Society, Dr. Mary H. Loveless of Cornell University Medical College, New York City, described her technique for a single subcutaneous injection for immunization against bee and wasp stings.

Dr. Aileen Ludington and her husband Dr. Louis, both graduates of the College of Medical Evangelists, Los Angeles, are resuming mission work at the Bangkok Sanitarium and Hospital in Thailand. Dr. Louis will be the medical director of the hospital and Dr. Aileen will be on the anesthesiology staff. Dr. Ethel R. Nelson, another CME graduate, is also on the staff.

Dr. Teresa McGovern of San Jose, Calif., recently became assistant clinical professor of medicine at Stanford University.

Dr. Eleanor G. Morris, elected Pennsylvania Medical Woman of the Year, 1960, was featured in an exclusive interview in *Scope Weekly* June 29. Providing medical service for Jones Mills, located in the mountains of Westmoreland County, involves Dr. Morris' making her house calls on skis when the mountainous country is snowbound. She serves a distance of 16 miles and sees about 160 patients weekly.

A senior at the University of Wisconsin Medical School, Madison, M. Therese Southgate, was awarded the Tallmadge prize for manifesting the greatest range of interest in the historical, cultural, and philosophical aspects of medicine. The awards were given at the Annual Field Day held April 29.

Marian Steinbauer of East Lansing won top scholastic honors in the freshman class at the University of Michigan Medical School, Ann Arbor, with a straight A average. The ratio of male to female students in the class is 20:1.

Dr. Irene T. Stemper of Oconomowoc was honored as a 50 year club member by the

Wisconsin Medical Society at its annual meeting earlier this year.

The Pennsylvania Public Health Association in the fall of 1959 presented their Merit award to DR. RUTH H. WEAVER of Philadelphia in recognition of her work "dedicated to improving the health of children."

At the meeting of the Women's Medical Society of New York State on May 8, DR. JANE C. WRIGHT, Assistant Attending Surgeon at University Hospital, discussed the paper, "Recent Advances in Chemotherapy Treatment of Cancer," presented by Dr. Ezra M. Greenspan. DR. FLORENCE C. H. CHU, Assistant Radiation Therapist at the Memorial Center for Cancer and Allied Diseases, presented "Radiotherapy Treatment in Cancer," which was discussed by DR. LUCILE E. LOSEKE, Director of Surgery at New York Infirmary.

AMWA PRESENTS . . .

The achievements of DR. MARGARET J. GIANNINI, a young pediatrician of New York City and a native of Haddonfield, N.J., were recently recognized by Amita, Inc., an organization dedicated to bringing recognition to American women of Italian origin, when they presented her with their Woman of the Year Award.

Dr. Giannini graduated with honors from Hahnemann Medical College, Philadelphia, in 1945. In 1950, at the age of 29 years, she began to work at the clinic for mentally retarded children at New York Medical College, Flower and Fifth Avenue Hospitals. This clinic was without precedent, and out of this pioneer work Dr. Giannini received her inspiration and an increasing desire to help retarded children. She has been administrative director of the clinic since its inception. Dr. Giannini is also assistant professor of pediatrics at New York Medical College, attending visiting pediatrician at Metropolitan Hospital, and consultant pediatrician at the Children's Cerebral Palsy Unit, Bird S. Coler Memorial Hospital.

A fellow of the American Academy of Pediatrics, she is on its Committee for Handicapped Children. She is also a diplomate of the American Board of Pediatrics and a member of the advisory board of the Kennedy Child Study Center, the American Association of Mental Deficiency, and the AMWA. She has participated in many radio and television programs, both in her capacity as pediatrician and as an expert on the mentally retarded child. She appeared on the radio program devoted to the "Emotional Health of the Family," sponsored by AMWA. In 1956 Dr. Giannini was selected as the pediatric expert for "World of Medicine." She appears in "Who's Who of American Women" and is the author of numerous publications and articles.

A well-traveled lecturer, Dr. Giannini most recently presented a paper to the Ninth International Pediatric Congress in Montreal, Canada. Her autumn schedule will take her

to meetings of the Association for Mental Deficiency, the Levenson Institute for Mental Deficiency, and the National Association of Mental Deficiency.

Dr. Giannini is devoted to her work and to her family, the latter consisting of her husband, Dr. Louis J. Salerno, Associate Professor of Obstetrics and Gynecology, New York Medical College, and four sons, aged 2, 4, 6, and 10 years. Her other interests include collecting stamps and antique china; participating in sports, especially swimming; painting watercolors; and attending the opera, to which she has had a season ticket for the past 10 years. For several years she wrote the "Doctor's Corner" for the *Hellenic-American*, an international monthly review. She is an avid fundraiser for scholarships for needy students.

AMWA is proud to present Dr. Giannini in this column.

Book Notices

Editor's Note: These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the JOURNAL.

THERAPEUTIC RADIOLOGY: Rationale, Technique, Results. By William T. Moss, M.D., Assistant Professor of Radiology, Northwestern University School of Medicine, Director, Department of Therapeutic Radiology, Chicago Wesley Memorial Hospital, and Chief, Department of Therapeutic Radiology, Veterans Administration Research Hospital, Chicago. Pp. 403, with 146 figures and 56 tables. Price $12.50. The C. V. Mosby Company, St. Louis, 1959.

This is a relatively small book, printed in large type on good quality paper. Physically it is a sturdy volume that will withstand the large amount of use it deserves, The arrangement of material is logical and the index fully adequate. The book contains all of the fundamentals, in what is very evidently an originally conceived arrangement. This appears to be the result of much clinical and teaching experience by a radiologist equipped with the ability of orderly, concise, and original thinking. There is no evidence that old information has been carried forward without thorough re-evaluation. The text places before the reader, in short well-chosen paragraphs, the particular problem under consideration in all of its important aspects. The safe dosage to the normal surrounding tissue, so often the limiting factor in the control of cancer, is prominantly featured in each category. This adds greatly to the value of the book.

In so young and rapidly changing a specialty it would be surprising if the reviewer completely agreed with all statements in the book. This, however, occurs often. The maxim of using the smallest effective dose in benign conditions would suggest that the recommended dose to keloids be somewhat reduced.

Whether through review, orientation, stimulation, or education, the reader, be he of another specialty, a radiological resident, or an experienced radiologist, will profit greatly through the availability of this book.

—*Carye-Belle Henle, M.D.*

ULCERATIVE COLITIS. By Harry E. Bacon, M.D., LL.D., F.A.C.S., F.A.C.P., Honorary Fellow, Royal Society of Medicine, Professor and Head of Department of Proctology, Temple University Medical Center, Philadelphia, President, American Board of Proctology, Diplomate, American Board of Surgery, and Member, Brazilian, Japanese, Philippine, and International colleges of surgeons. Pp. 395, with 184 illustrations. Price $15.00. J. B. Lippincott Company, Philadelphia, 1958.

This exhaustive monograph on ulcerative colitis covers the disease from every angle—it includes chapters on history, etiology, pathology, diagnosis, complications, and treatment. It is written by a surgeon from the surgeon's point of view. Over and over again emphasis is placed on the severity of the lesions found in the colon either in proctoscopic examination or in the surgical specimen. The reader is left with the impression that lesions of such magnitude are irreversible and cannot possibly yield to conservative forms of treatment.

The chapter on Nonsurgical Treatment comprises only 43 of the book's 396 pages. It states the following: "At the present time there is no specific nonsurgical form of treatment. But ulcerative colitis can be cured by surgical removal of the diseased bowel." The author quotes his own series of 400 patients, covering a 16 year period, to show that the results achieved by expert medical and psychiatric care have been unimpressive. However, he does state that in 60 per cent of cases the patient may improve or the disease may be controlled by an experienced physician.

Although short, the chapter on Nonsurgical Treatment is quite exhaustive, as it includes old and new forms of therapy and contains a special reference to psychotherapy. In this respect the author feels that the patient's own physician who sees him daily and knows him best should serve in the capacity of psychiatrist.

The chapters on surgical treatment comprise a good half of the treatise. The indications for surgery, according to Bacon, are: acute fulminating or toxic ulcerative colitis, chronic ulcerative colitis of moderate severity that does not respond to medical treatment, and complications of systemic or surgical nature.

Special stress is placed on the danger of carcinomatous degeneration if a diseased colon is not removed. The techniques of ileostomy are carefully described and the importance of a good stoma for the patient's further life is especially emphasized.

The eight radical procedures are classified and discussed at length and there are five charts containing the author's own statistics on 440 patients who underwent five different radical surgical procedures.

Of outstanding importance is the diligence and care that the author gives to the patient who has to live with his ileostomy. There is a chapter on the ileostomy bag, in which every existing type of bag is described: their materials, advantages, and disadvantages are thoroughly discussed, and even the manufacturer's names, places of availability, and prices are

listed. There is also a list of commercially available equipment, useful to the patient who has had an ileostomy, and the chapter, The Patient and His Ileostomy Life, teaches how to help and guide the patient to adjust to his ileostomy and to lead a normal life in every respect. These chapters make this book important not only for the surgeon but also for every physician who cares for patients with ulcerative colitis.

A chapter on the special anesthetic problems occurring in the patient with ulcerative colitis during radical surgery is contributed by an anesthetist.

—Ruth W. Sherwin, M.D.

PROCEEDINGS OF THE THIRD NATIONAL CANCER CONFERENCE, Detroit, Mich., June 4-6, 1956, sponsored by the American Cancer Society, Inc., and the National Cancer Institute, U.S. Public Health Service. Pp. 961. Price $2.50. J. B. Lippincott Co., Philadelphia, 1957.

The account of the Third National Conference is divided like Gaul into three parts: (1) opening and closing remarks, (2) general lectures, and (3) symposia and panels. Part 1 deserves careful reading as it deals with specific as well as general observations in regard to cancer research and achievements in the field. There are chapters on epidemiology, radiation neoplasia, virus etiology, and measurement of morbidity by well-known workers from many important centers of research. The chapter entitled Factors Influencing the Curability of Cancer by Fred W. Stewart of Memorial Hospital is an excellent, scholarly, witty, and thoroughly honest resumé of the work of the past 15 years. Chapters on various cancer sites of the body are competent and the authors are generally well known for their experience and studies. Surgeons, pathologists, biochemists, cytologists, radiologists, internists, statisticians, and research workers in their presentations and discussions provide excellent material for study. One chapter on the popular subject of smoking and pulmonary cancer is a thorough review of this controversial problem. The work of Michael Jordan, Genevieve Bader, and Emerson Day, of Strang Clinic and Sloan-Kettering Institute, on carcinoma in situ showed interesting results of diagnostic observations in 53 patients.

This volume contains a wealth of information on all phases of diagnosis, treatment, and research and is a veritable encyclopedia of the subject, presented by the best qualified schools and research centers of the United States, Europe, and Japan. The illustrations, graphs, and tables aid greatly in understanding the various aspects of this popular but confusing subject.

—Frances H. Bogatko, M.D., F.A.C.S.

POISONING: A GUIDE TO CLINICAL DIAGNOSIS AND TREATMENT. Ed. 2. By W. F. von Oettingen, M.D., Ph.D., National Institutes of Health, U.S. Public Health Service, U.S. Department of Health, Education, and Welfare. Pp. 627. Price $12.50. W. B. Saunders Company, Philadelphia, 1958.

The book is divided into four parts: (1) classification of poisons, the medicolegal aspects and responsibilities of the physician, and the emergency measures and equipment necessary for the treatment of poisoning; (2) clinical diagnosis of poisoning; (3) management of poisoning, such as techniques available for removal of toxic agents and the symptomatic treatment; and (4) alphabetical listing of poisons.

With the introduction of numerous new therapeutic agents (some with potentially dangerous side effects) knowledge regarding these is of vital importance in correct diagnosis and treatment of the patient. This book aims to supply in a single source information needed by the clinician for the accurate detection and successful treatment of poisoning.

—Judith Cohen, B.S., R.P.
Chief Pharmacist, New York Infirmary

REVERSICON: A Medical Word Finder. J. E. Schmidt, Ph.B.S., M.D., Litt. D., President of The American Society of Grammatolators, and Chairman, National Association on Standard Medical Vocabulary. Pp. 440. Price $7.50. Charles C Thomas, Publisher, Springfield, Ill., 1958.

Standard dictionaries list words in alphabetical order and give their meaning. This dictionary differs from the conventional lexicon by listing ideas, or concepts, and allowing one to find the scientific term to fit them.

The definitions are placed in order of the principal word of the idea: for instance, under the word "food" are listed 50 different ideas having to do with the subject. To quote a few of them: "food and drink, condition of body resulting from extreme deprivation of—inanition; food, aversion for—apositia; food, chewed and prepared by mouth for swallowing—bolus; food, excessive intake of—hyperalimentation; food, material of a seed—endosperm; food, scheme or system for taking—dietary."

Medical writers try to be accurate in their use of scientific terms, but they frequently do not know the exact word that would express their meaning. This "reversed dictionary," will be a great boon in helping them to find the word they want. Once they have become accustomed to looking up a concept rather than a word they will want to have this most interesting volume on their desks at all times.

—Camille Mermod, M.D.

SURVEY OF CLINICAL PEDIATRICS. Ed. 3. By Lawrence B. Slobody, M.D., Professor of Pediatrics, New York Medical College, Director of Pediatrics, Flower and Fifth Avenue Hospitals and Metropolitan Hospital, and Medical Director, Children's Center, New York City. Pp. 556, with 5 figures and 34 tables. Price $11.00. The Blakiston Division, McGraw-Hill Book Company, Inc., New York, 1959.

This third edition of a brief survey of highlights of pediatrics comes only four years after the second edition, but new material on therapy, nutrition, immunization, and congenital heart disease has increased the size by over 50 pages. It will be even more useful to students and others than the former editions and the librarian will have even more trouble keeping it available for all!

—Josephine G. Nichols, Librarian,
New York Infirmary

Books Received

The following books have been received for review and are acknowledged in this column. More detailed reviews will be published on books of most interest to our readers and as space permits.

ANTIBIOTICS IN MEDICINE. *British Medical Bulletin*, Vol. 16, No. 1, Jan., 1960. Pp. 88, with illustrations. Price $3.25. Medical Department, The British Council, London, England.

Contributions to this symposium include the clinical aspects of preventive administration in medicine and surgery and separate consideration of antibiotic therapy in tuberculosis and bacterial endocarditis; chemical nature and classification, pharmacology, methods of employment, and behavior in the body of antibiotics; acquired bacterial resistance; technical discussion on the determination of bacterial sensitivity; employment of antibiotics in selective culture media and interaction between the antibiotic and the individual cell; and combined therapy.

BIBLIOGRAPHY ON BILHARZIASIS, 1949-1958. Pp. 158. Price $2.00. World Health Organization, U.S. Distributor, Columbia University Press, New York, 1960.

CHILDBIRTH WITHOUT PAIN. By Dr. Pierre Vellay and others. Translated by Denise Lloyd. Pp. 216, with illustrations. Price $3.95. E. P. Dutton & Co. Inc., New York, 1960.

COMMUNICABLE DISEASES IN SCHOOLS: Survey of Existing Legislation. Offprint from *International Digest of Health Legislation*, Geneva, Vol. 10, No. 2, Pp. 66. Price $0.70. World Health Organization, Geneva, Switzerland, 1959.

DR. SCHMIDT'S BABY NAME FINDER. By J. E. Schmidt, M.D., Litt.D., President, The American Society of Grammatolators, and Chairman, National Association on Standard Medical Vocabulary. Pp. 390, with illustrations. Price $10.50. Charles C Thomas, Publisher, Springfield, Ill., 1960.

GROWING UP TO LOVE, SEX AND MARRIAGE. By Sidney L. Sands, M.D. Pp. 131. Price $3.00. Christopher Publishing House, Boston, 1960.

MATERNAL DISORDERS RELATED TO FETAL STRESS, PERINATAL DEATH AND CONGENITAL DEFECTS. Selected References 1952-58. Compiled by Elizabeth Koenig, Reference Librarian, NIH Library, Division of Research Services. Public Health Service Publication No. 669; Public Health Bibliography Series No. 25. Pp. 33. Price $0.15. U.S. Government Printing Office, Washington, D.C., 1959.

THE MIND OF YOUR CHILD. By Doris Odlum, M.R.C.S., L.R.C.P. D.P.M. Pp. 108. Price 4s. W.&G. Foyle Ltd., London, England, 1960.

PERSPECTIVES IN PEDIATRIC VIROLOGY. Report of the Thirty-Third Ross Conference on Pediatric Research, held under the auspices of the Research Foundation of The Children's Hospital of the District of Columbia and the Department of Pediatrics of Georgetown University, Washington, D.C., Feb. 26-27, 1959. Pp. 91. Ross Laboratories, Columbus, Ohio.

PRINCIPLES OF BIOCHEMISTRY. Ed. 2. By Abraham White, Ph.D., Professor of Biochemistry, Albert Einstein College of Medicine, Yeshiva University, New York City; Philip Handler, Ph.D., Professor of Biochemistry and Nutrition, Duke University School of Medicine, Durham, N.C.; Emil L. Smith, Ph.D., Professor of Biological Chemistry and Research Professor of Medicine, University of Utah College of Medicine, Salt Lake City; and DeWitt Stetten, Jr., M.D., Ph.D., Associate Director in Charge of Research, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md. Pp. 1,149, with figures. Price $15.00. The Blakiston Division, McGraw-Hill Book Company, Inc., New York, 1959.

RADIOLOGIC RECORDS. By Sister Christina Spirko, C.S.J., R.T., B.S. in R.T., M.A., F.A.S.X.T., Department of Roentgenology, St. Mary's Hospital, Instructor in Sociology, St. Mary's School, Amsterdam, New York, and Editor, X-ray column, *Hospital Management*, Chicago. Pp. 304, with illustrations. Price $8.50. Charles C Thomas, Publisher, Springfield, Ill., 1960.

RESEARCH ACTIVITIES. New York University-Bellevue Medical Center. Compiled by Everett J. Elmer, Coordinator of Research Grants. Pp. 124. 1958. Copies available from the Office of Development, Public Relations, NYU-Bellevue Medical Center, 550 First Ave., New York City.

TUBERCULOSIS—A CURRENT COMPARISON OF HOME AND SANITORIUM TREATMENT OF PULMONARY TUBERCULOSIS IN SOUTH INDIA. *Bulletin of the World Health Organization*. Vol. 21, No. 1, 1959. Pp. 144, with illustrations. Price $2.00. World Health Organization, Geneva, Switzerland.

WORLD HEALTH ORGANIZATION TECHNICAL REPORT SERIES: No. 166—Effect of Radiation on Human Heredity: Investigations of Areas of High Natural Radiation; No. 178—Requirements for Biological Substances: (1) General Requirements for Manufacturing Establishments and Control Laboratories and (2) Requirements for Poliomyelitis Vaccine (Inactivated); No. 181—Immunological and Haematological Surveys; No. 183—Mental Health Problems of Automation; No. 190—Expert Committee on Venereal Infections and Treponematoses; No. 193—Teacher Preparation for Health Education; No. 194—Local Health Service; No. 198—European Technical Conference on the Control of Infectious Diseases Through Vaccination Programmes. Price $0.30; No. 194, $0.60; and No. 190, $1.00. World Health Organization, Geneva, Switzerland; No. 166-183, 1959; No. 190-198, 1960.

YOUR MIND CAN MAKE YOU SICK OR WELL. By C. S. Wachtel, M.D. Pp. 244, with 3 figures. Price $4.95. Prentice-Hall, Inc., Englewood Cliffs, N. J., 1959.

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—Natenshon, A. L.: Dis. Nerv. System *17*:392 (Dec.) 1956.

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—Pennington, V. M.: Mississippi Doctor *35*:57 (Aug.) 1957.

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1. Franklin, M., et al.: Chelate Iron Therapy, J. A. M. A. 166:1685, 1958.
2. A. M. A Council on Drugs: New and Nonofficial Drugs, J. A. M. A. 171:891, 1959.
3. A. M. A. Committee on Toxicology: Accidental Iron Poisoning in Children J. A. M. A. 170:676, 1959

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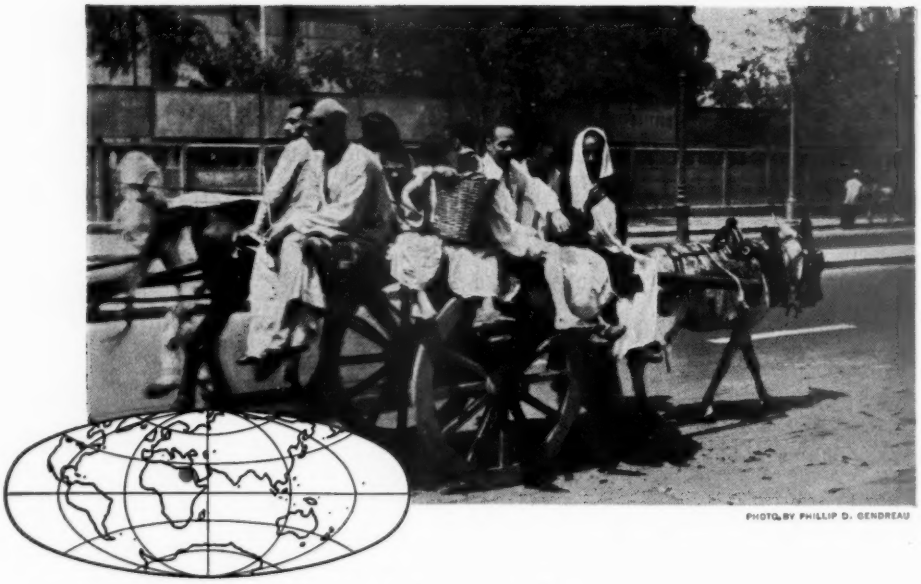

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Cairo investigators administered FUROXONE for one week to 37 patients with shigellosis, reported all 37 clinically cured, 35 free of shigella prior to completion of FUROXONE therapy.

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Musgrave, M. E. and Arm, H. G.: Antibiotic Med. & Clin. Therapy 7:17 (Jan.) 1960.

FUROXONE LIQUID: a pleasant orange-mint flavored suspension containing FUROXONE 50 mg. per 15 cc., with kaolin and pectin ■ for patients of all ages (may be mixed with infant formulas, passes through a standard nursing nipple) ■ Supply: bottles of 240 cc. **FUROXONE TABLETS:** 100 mg., scored, bottles of 20 and 100.

DOSAGE: should provide (in 4 divided doses) 400 mg. daily for adults, 5 mg./Kg. daily for children.

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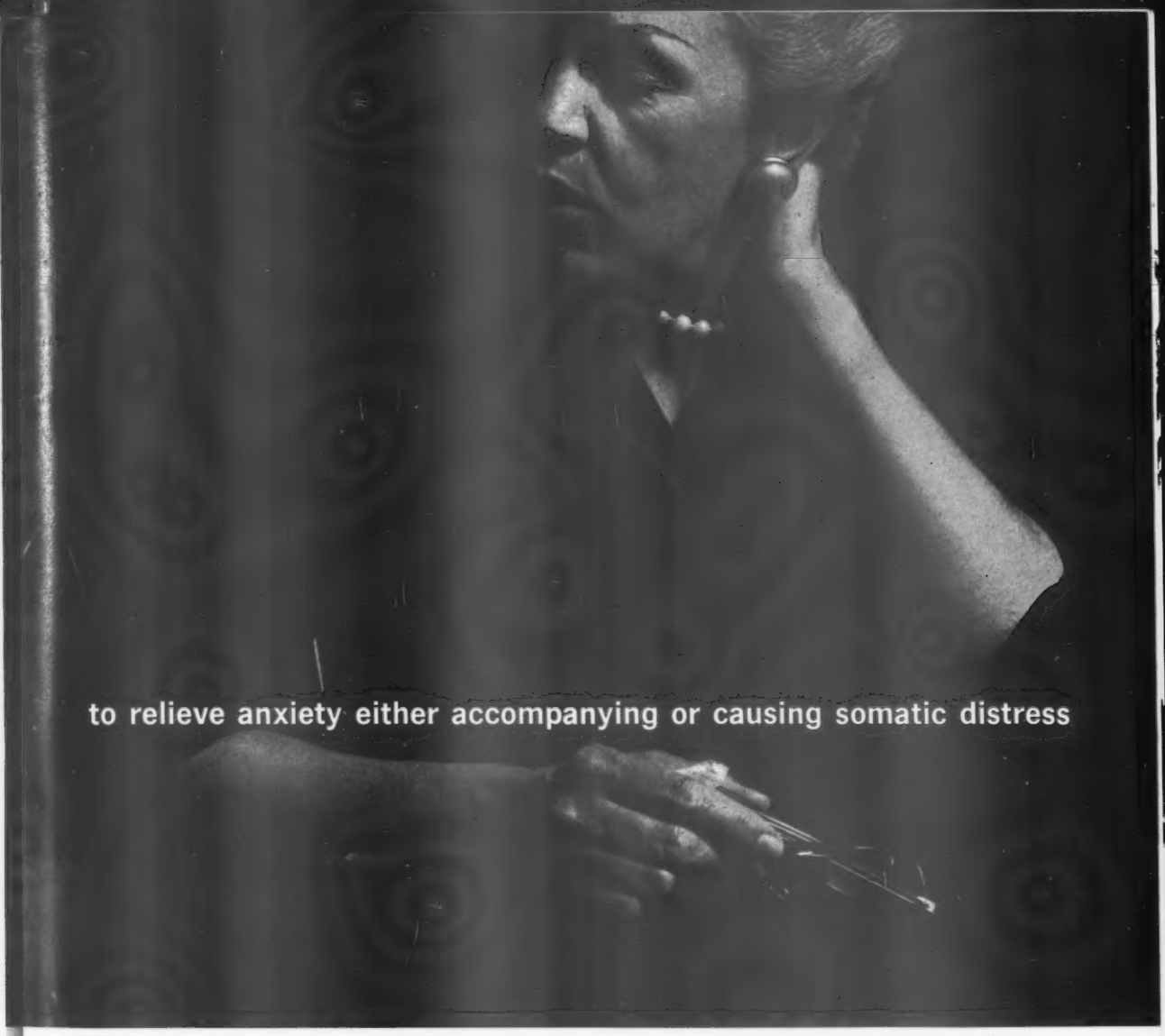

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N.B.: For further information on dosage, side effects, cautions and contraindications, see available comprehensive literature, *Physicians' Desk Reference,* or your S.K.F. representative. Full information is also on file with your pharmacist.

1. Marx, F.J., in *Trifluoperazine: Further Clinical and Laboratory Studies*, Philadelphia, Lea & Febiger, 1959 p. 89
2. Winkelman, N.W., Jr.: *ibid.*, p. 78.

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raises pain threshold

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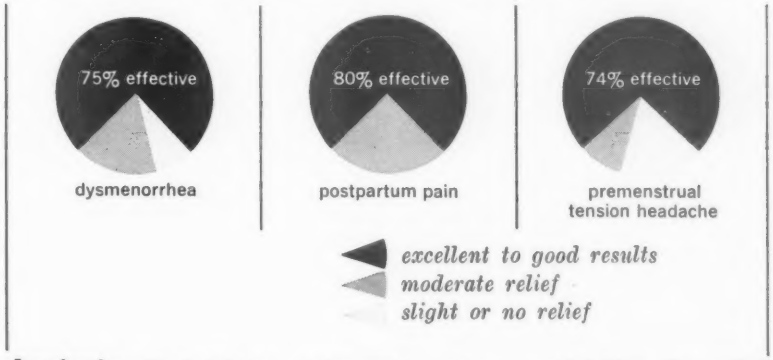

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1. Gray, A. P., *et al.*: Am. Chem. Soc. *81*:4347, 1959. 2. O'Dell, T. B.: Ann. New York Acad. Sc. *86*:191, 1960. 3. O'Dell, T. B., *et al.*: J. Pharmacol. & Exper. Therap. *128*:65, 1960. 4. O'Dell, T.B., *et al.*: Fed. Proc. *18*:1694, 1959. 5. Batterman, R. C., *et al.*: Am. J. Med. Sc. *238*:315, 1959. 6. Wainer, A. S.: Ann. New York Acad. Sc. *86*:250, 1960.

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Cobalt is the only clinically proved therapeutic agent which enhances the formation of erythropoietin, the hormone which regulates erythropoiesis in the body.[1-3]

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The result is a more rapid and complete hematologic response in the anemic patient . . .[5-9]

and because...

The safety of Roncovite has been thoroughly attested in published literature and demonstrated during the administration of over 365 million doses.[6,10,11]

1. Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood *13*:55 (Jan.) 1958. 2. Murdock, H. R. Jr.: Am. Pharm. Assoc. (Sci. Ed.) *48*:140, 1959. 3. Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L.: Science *125*:1085 (May 31) 1957. 4. Center, W. M.: Clin. Med. *7*:713 (April) 1960. 5. Holly, R. G.: Obst. & Gynec. *9*:299 (Mar.) 1957. 6. Ausman, D. C.: Journal-Lancet *76*:290 (Oct.) 1956. 7. Flynn, R. T.: Therapy with Cobalt and Iron for Correction of Anemia in Pregnancy, Presented at Michigan and Wayne Co. Acad. GP, Postgrad. Clinic, Detroit, Mich., Nov. 11-12, 1959. 8. Tevetoglu, F., and Ozkaragoz, K.: M. Times *86*:81 (Jan.) 1958. 9. Craig, P. E.: Clin. Med. *6*:597 (April) 1959. 10. Hill, J. M.; LaJous, J., and Sebastian, F. J.: Cobalt Therapy in Anemia, Texas J. Med. *51*:686 (Oct.) 1955. 11. Tevetoglu, F.: J. Pediat. *49*:46 (July) 1956.

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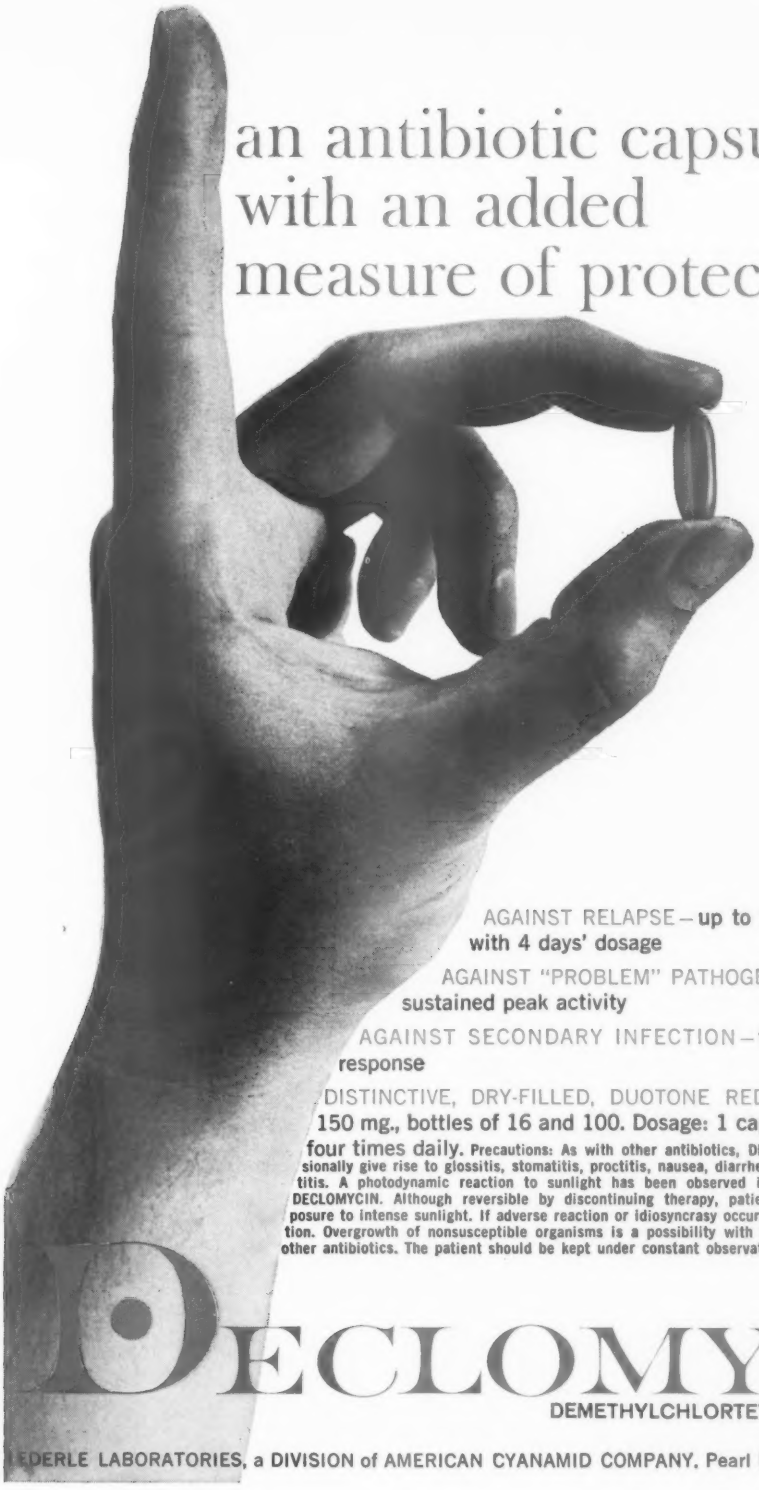

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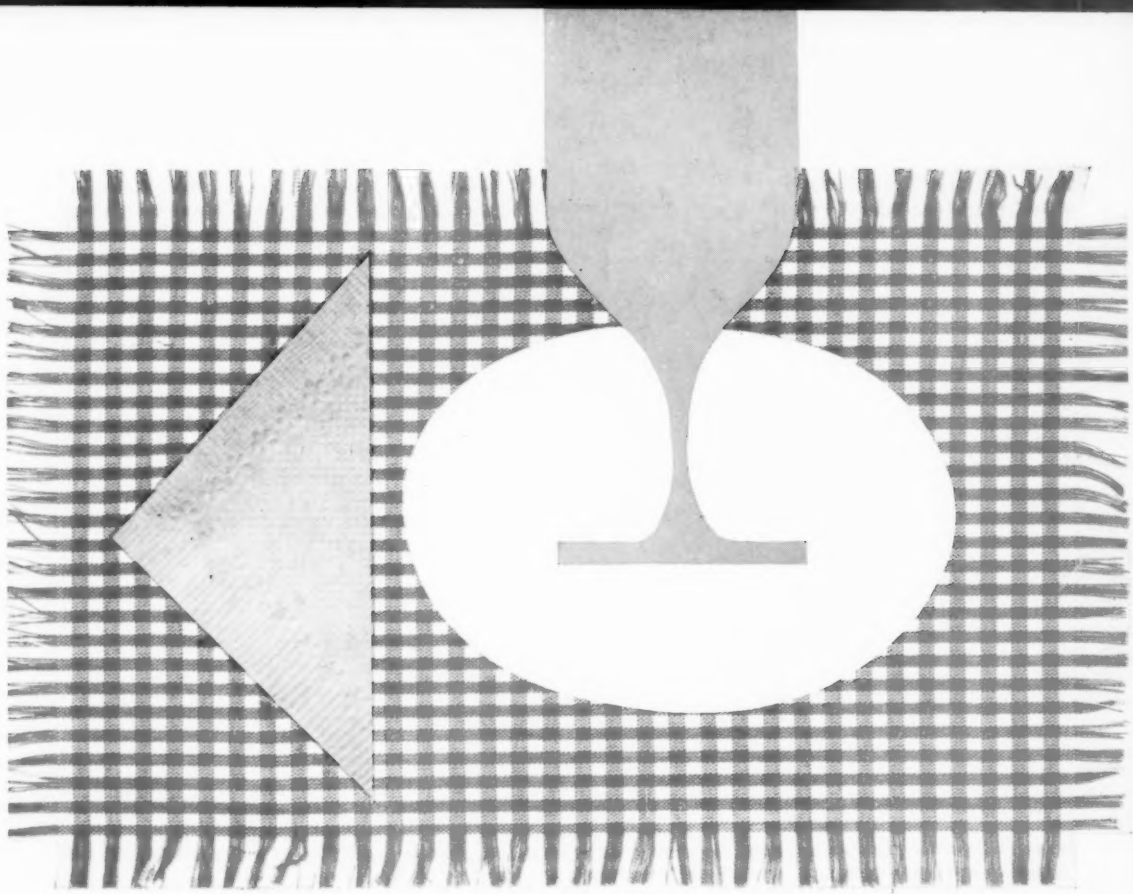

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